

Evaluation of long-term safety and efficacy of omalizumab in elderly patients with uncontrolled allergic asthma



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ABSTRACT

Background: Severe asthma management in elderly patients may be difficult because of increased comorbid conditions, polypharmacy, physiologic changes that occur with aging, incorrect use of inhaler devices, and poor adherence.

Objective: To evaluate the long-term safety and efficacy of the anti-IgE antibody omalizumab in elderly (aged ≥ 65 years) patients with uncontrolled allergic asthma.

Methods: The efficiency and adverse effects of omalizumab treatment were evaluated based on data extracted from medical records. Patients were evaluated monthly for efficacy and adverse reactions. Treatment efficacy was evaluated by level of asthma symptom control, using the Global Initiative for Asthma guideline.

Results: Nineteen consecutive elderly patients with asthma (female to male ratio, 14:5) formed our cohort. The mean (SD) age, disease duration, and total IgE level were 69.3 (5.8) years, 19.4 (8.6) years, and 299.1 (197.2) IU/mL, respectively. The mean (SD) duration of omalizumab treatment was 35.6 (17.8) months (range, 9–66 months). All the patients had at least 1 perennial inhalant allergen sensitivity and had uncontrolled allergic asthma. Elderly patients experienced no significantly important adverse reaction considered to be related to omalizumab treatment. Only 1 patient had a local adverse reaction and 1 had myalgia that was considered to be drug related. After omalizumab treatment, asthma symptoms were well controlled in 9 patients (47.4%) and partly controlled in 8 patients (42.1%). Two of the patients (10.5%) still had uncontrolled asthma.

Conclusion: Our study found that omalizumab is a well-tolerated and effective therapy for elderly patients with uncontrolled asthma.

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Introduction

Asthma affects an estimated 300 million individuals worldwide and is an important global health problem that affects all age groups, with increasing prevalence in many developing countries, increasing treatment costs, and an increasing burden for patients and the community.¹ Most of these patients have uncontrolled asthma, and a significant proportion of severe cases are related to allergic IgE-mediated mechanisms. The anti-IgE treatment omalizumab is a recombinant humanized monoclonal antibody used for patients with uncontrolled moderate or severe allergic asthma and is both effective and safe.^{2–7}

In elderly patients with asthma lung function usually decreases because of the longer duration of asthma, increasing age and

stiffness of the chest wall, reduced respiratory muscle function, loss of elastic recoil, and airway wall remodeling. Older patients may not report asthma symptoms, and they may attribute their asthmatic symptoms to normal aging or comorbidities, such as cardiovascular disease and obesity.^{8–10} Comorbid arthritis may lead to decreased exercise capacity and lack of fitness and may also hinder correct use of inhalers. In addition, asthma may have higher costs in older patients because of increased hospitalization rates and multiple medication prices because of comorbidities.⁹

Management of asthma in older people is difficult because of the effects of comorbidities, polypharmacy, and lack of self management skills. Given these problems, standard symptom control and risk minimization goals must be carefully addressed.^{8,9} Adverse effects of β_2 -agonists, such as cardiotoxicity, and corticosteroid adverse effects, such as osteoporosis, are more common in elderly people than in younger adults, and the theophylline doses must be reduced in the elderly people.⁸

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Reviews and meta-analyses have found that omalizumab therapy does not increase the overall incidence of adverse events,^{11,12} but data on the long-term efficacy and safety of asthma medications in the elderly population are limited because these patients are often excluded from major clinical trials.

The aim of this study was to evaluate the safety and efficacy of omalizumab. We report our real-life experience with omalizumab in elderly patients with uncontrolled allergic asthma who had increased IgE levels and were sensitive to at least 1 perennial allergen.

Methods

Patients and Study Design

A total of 7,532 patients with asthma have been evaluated in our outpatient clinic since 2010. Sixty of them who had severe persistent allergic asthma sensitive to at least 1 perennial allergen were treated with omalizumab. Nineteen of these patients were older than 64 years old and might be classed as being elderly (Fig 1).

Their diagnoses and therapies were appropriate according to the recent Global Initiative for Asthma (GINA) guideline.¹³ Omalizumab therapy was given according to the Ministry of Health's criteria in Turkey. Before omalizumab therapy commenced, all patients were taking high doses of inhaled corticosteroids (ICSs), long-acting β -adrenoreceptor agonists (LABAs), and leukotriene receptor antagonists (LTRAs). Despite this combined therapy, asthma symptoms in the elderly patients remained uncontrolled. Therefore, omalizumab therapy was started.

Dosages for omalizumab therapy were based on a patient's baseline total IgE level and weight according to the dosage guide for omalizumab. Omalizumab was administered by subcutaneous injection. All patients were observed for adverse effects for at least 2 hours after being given the injection. They were also told of the possibility of a delayed reaction and had the ability to recognize the signs and symptoms of anaphylaxis.

Patients were evaluated monthly for adverse reactions and efficacy. Treatment efficacy was evaluated by level of asthma symptom control as well controlled, partly controlled, and uncontrolled based on the assessment of asthma control in adults of the GINA guideline.¹³ Spirometry was performed at the start of treatment and then every 3 months. The data for this study were taken from patients' files. The study was approved by Antalya Training and Research Hospital Ethics Committee.

Statistical Analysis

Descriptive statistics were used, and the results were expressed as mean (SD). Wilcoxon test was used to compare the parameters of before and after omalizumab treatment. $P < .05$ was considered statistically significant.

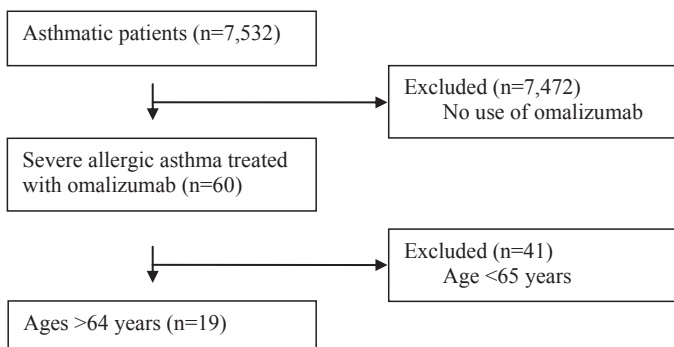


Figure 1. Flow diagram of asthmatic patients.

Results

Baseline demographic and clinical characteristics of the patients are given in Table 1. There have been 19 patients older than 64 years in whom omalizumab therapy has been started in our outpatient clinic since 2010. All 19 patients were included in the study. The mean (SD) age of these patients was 69.3 (5.8) years (range, 65–87 years), and most patients were women ($n = 14$ [73.6%]). The mean (SD) total IgE levels and asthma duration were 299.1 (197.2) IU/mL and 19.4 (8.6) years, respectively. Sixteen patients had dust mite allergy, and 3 patients had other inhalant perennial allergen sensitivity. The mean (SD) duration of omalizumab therapy was 35.6 (17.8) months (range, 9–66 months). Omalizumab dosage was 150 mg/mo in 3 patients, 225 mg/mo in 1 patient, 300 mg/mo in 3 patients, 225 mg every 15 days in 6 patients, 300 mg every 15 days in 3 patients, 375 mg every 15 days in 2 patients, and 450 mg every 15 days in 1 patient based on their pretreatment serum total IgE concentration and body weight.

There was hypertension in 9 patients (47.4%), diabetes mellitus in 3 (15.8%), osteoporosis in 5 (26.3%), chronic obstructive pulmonary disease (COPD) in 2 (10.5%), atrial fibrillation in 3 (15.8%), benign prostatic hyperplasia in 1 (5.3%), chronic hepatitis B in 1 (5.3%), and hypothyroidism in 1 (5.3%) as comorbidities. Two patients (10.5%) were ex-smokers, and 1 (5.3%) is a current smoker.

Before omalizumab treatment commenced, all patients had uncontrolled asthma despite high doses of ICSs, LABAs, and LTRAs. After omalizumab treatment, the mean (SD) numbers of asthma exacerbations (4.12 [1.61] vs. 0.53 [1.28]) ($P < .001$) and hospitalizations (1.12 [1.05] vs. 0.23 [0.75]) ($P = .004$) were significantly reduced. Most of the patients ($n = 17$ [89.4%]) experienced significantly lower rates of asthma exacerbation and hospitalization. Their asthma symptom control levels improved. After omalizumab treatment, asthma symptoms were well controlled in 9 patients (47.4%) and partly controlled in 8 patients (42.1%). Two patients (10.5%) still had uncontrolled asthma (Fig 2). The mean (SD) asthma control test score was significantly increased compared with the basal score (10.44 [3.47] vs. 21.8 [3.82]) ($P < .001$). There was improvement in pulmonary function tests, but the change in

Table 1

Baseline Demographic and Clinical Characteristics of the 19 Study Patients

Characteristic	Finding
Age, mean (SD), y	69.3 (5.8)
Female, No. (%)	14 (73.6)
Weight, mean (SD), kg	73.7 (7.9)
Total IgE, mean (SD), IU/mL	299.1 (197.2)
Duration of asthma, mean (SD), y	19.4 (8.6)
FEV ₁ , mean (SD), L (%)	1.21 (0.45) (54.8 [20.8])
Skin test positivity, No. (%)	
Dust mites	16 (84.2)
Mold	3 (15.8)
Grass pollen	1 (5.3)
Animal dander	2 (10.5)
Comorbidity, No. (%)	
Hypertension	9 (47.4)
Diabetes mellitus	3 (15.8)
Osteoporosis	5 (26.3)
COPD	2 (10.5)
Atrial fibrillation	3 (15.8)
Benign prostatic hyperplasia	1 (5.3)
Chronic hepatitis B	1 (5.3)
Hypothyroidism	1 (5.3)
Smoking, No. (%)	
Nonsmoker	16 (84.2)
Ex-smoker	2 (10.5)
Current smoker	1 (5.3)
Omalizumab duration, mean (SD), mo	35.6 (17.8)

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second.

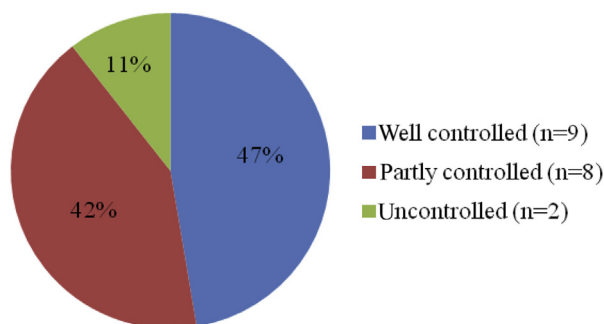


Figure 2. Levels of asthma symptom control of patients after omalizumab treatment.

percentage of forced expiratory volume in 1 second was not significant (54.84 [20.82] vs 67.01 [25.56]) ($P = .11$).

Adverse Reactions

Adverse event reports during omalizumab treatment were evaluated. Only 1 patient had local adverse reactions, and 1 had myalgia that was considered to be drug related. One patient aged 77 years who had uncontrolled allergic asthma died of bronchial cancer. There were no significant systemic adverse reactions related to omalizumab use; in particular, there were no anaphylactic major adverse reactions. Treatment with omalizumab was well tolerated. There were no clinically significant abnormalities found during the physical examination of the patients during omalizumab treatment.

Discussion

This study provides evidence that omalizumab is a safe and effective therapy for elderly patients with severe allergic asthma. To our knowledge, this is the first study to evaluate the long-term safety and efficacy of omalizumab in elderly (≥ 65 years old) patients with uncontrolled allergic asthma in real-life conditions. Prior studies and reviews have found that omalizumab is an effective and safe therapy option for moderate to severe allergic asthma. However, evidence for its long-term (>1 year) safety in adults is very limited. In recent years, new reviews have assessed the efficacy and safety of omalizumab in the long term in both adults and children with allergic asthma that is poorly controlled despite treatment with high doses of ICSs or ICSs plus LABAs.^{11,12,14}

Drug therapy is an important issue in the treatment of elderly patients. Polypharmacy is common in this age group because of the increased number of diseases. The presence of multiple diseases creates a complicated clinical situation because of the effects and adverse effects of diseases and drug interactions. Factors such as age-related changes in pharmacokinetics and pharmacodynamics, interindividual variability, reduced homeostatic mechanisms, frailty, and psychosocial issues need to be evaluated when drug interactions are identified.¹⁵

Adherence to medications is also an important point in the elderly population because there are multiple, complex drug regimens, adverse effects, and cognitive impairment.¹⁶ Cognitive impairment is especially important in this age group in whom forgetfulness leads to inadequate therapy on one hand and drug toxicity attributable to errors in use on the other. As a result, omalizumab administered once or twice a month is a very good choice for elderly patients, given the adherence issue.

In our study, only 2 elderly patients (10.5%) continued to have uncontrolled asthma after omalizumab treatment. Thus 89.5% of patients had improvement after omalizumab treatment. Two of the patients who had partly controlled asthma also had COPD. They

thus had asthma-COPD overlap syndrome according to recent guidelines.¹⁷ The efficacy of omalizumab in treating this condition has recently been reported in a case series.¹⁸

The literature contains many clinical trials and real-life studies about the safety of omalizumab. In a review in which 7 randomized clinical trials and 18 real-life studies on omalizumab in severe allergic asthma were analyzed, real-life studies provided a significantly longer follow-up duration than randomized clinical trials (18.29 vs 8.57 months), which gives a better indication of clinical practice.¹⁴ In our study, the mean (SD) duration of omalizumab treatment was 35.6 (17.8) months (range, 9–66 months), which was much longer than in other studies. Real-life studies presumably allow a more correct assessment of the long-term safety of treatment with omalizumab as well. Romand et al¹⁹ found that omalizumab might be an effective and well-tolerated therapeutic option for elderly patients with inadequately controlled severe allergic asthma in 2 patients older than 75 years. In addition, Korn et al²⁰ confirm the clinical efficacy of omalizumab in patients with severe allergic asthma irrespective of age in a real-life setting.

In terms of adverse events, myalgia that was considered to be drug related was seen in only 1 patient, but there were no problems identified during her clinical examination or follow-up. A local adverse reaction was seen in 1 patient. There were no significant systemic adverse reactions related to omalizumab use, such as anaphylaxis. Therefore, omalizumab treatment was not stopped. Treatment with omalizumab was well tolerated. Nevertheless, 1 patient aged 77 years who had uncontrolled allergic asthma died because of bronchial cancer. She was a nonsmoker and had been using omalizumab for 40 months. No association between omalizumab treatment and risk of malignancy has been reported in the literature to date. In an epidemiologic study of omalizumab, malignancy rates were similar in the omalizumab and nonomalizumab cohorts, with a rate ratio of 0.84 (95% CI, 0.62–1.13) for all malignant tumors and 0.98 (95% CI, 0.71–1.36) for all malignant tumors, excluding nonmelanoma skin cancer.²¹ In another study, Busse et al²² found that there was no association between omalizumab treatment and risk of malignancy in a randomized, double-blind, placebo-controlled trial.

Our study has a few limitations. The cohort size is small and most patients are women, so the study group is not homogeneous. Our study was conducted in a single center as a pilot study, which might be another limitation. On the other hand, the long duration of follow-up and the first report of safety and efficacy data in a highly selected population are its strengths. In addition, retrospective analyses are important because they reflect real-life conditions and patients are clinically heterogeneous.

To our knowledge, this is the first real-life safety study that specifically addresses patients older than 64 years with severe allergic asthma. Our data indicate that omalizumab is safe and effective in elderly patients with severe allergic asthma under real-life conditions. However, it is clear that further studies of larger cohorts are needed.

References

- [1] Pocket Guide for Asthma Management and Prevention. Global Initiative for Asthma (GINA) Report 2016. <http://www.ginasthma.org/2016-pocket-guide-for-asthma-management-and-prevention/>. Accessed June 26, 2016.
- [2] Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev*. 2014;1:CD003559.
- [3] Ayres J, Higgins B, Chilvers E, Ayre G, Blogg M, Fox H. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. *Allergy*. 2004;59:701–708.
- [4] Buhl R, Hanf G, Soler M, et al. The anti-IgE antibody omalizumab improves asthma-related quality of life in patients with allergic asthma. *Eur Respir J*. 2002;20:1088–1094.

- [5] Luskin AT, Kosinski M, Bresnahan BW, Ashby M, Wong DA. Symptom control and improved functioning: the effect of omalizumab on asthma-related quality of life (ARQL). *J Asthma*. 2005;42:823–827.
- [6] Karpel J, Massanari M, Geba GP, Kianifard F, Inhaber N, Zeldin RK. Effectiveness of omalizumab in reducing corticosteroid burden in patients with moderate to severe persistent allergic asthma. *Ann Allergy Asthma Immunol*. 2010;105:465–470.
- [7] Kulus M, Hebert J, Garcia E, Fowler Taylor A, Fernandez Vidaurre C, Blogg M. Omalizumab in children with inadequately controlled severe allergic (IgE-mediated) asthma. *Curr Med Res Opin*. 2010;26:1285–1293.
- [8] Reed CE. Asthma in the elderly: diagnosis and management. *J Allergy Clin Immunol*. 2010;126:681–687.
- [9] Gibson PG, McDonald VM, Marks GB. Asthma in older adults. *Lancet*. 2010;376:803–813.
- [10] Slavin RG, Haselkorn T, Lee JH, et al. Asthma in older adults: observations from the epidemiology and natural history of asthma: outcomes and treatment regimens (TENOR) study. *Ann Allergy Asthma Immunol*. 2006;96:406–414.
- [11] Lai T, Wang S, Xu Z, et al. Long-term efficacy and safety of omalizumab in patients with persistent uncontrolled allergic asthma: a systematic review and meta-analysis. *Sci Rep*. 2015;5:8191.
- [12] Corren J, Casale T, Lanier B, Buhl R, Holgate S, Jimenez P. Safety and tolerability of omalizumab. *Clin Exp Allergy*. 2009;39:788–797.
- [13] Global Strategy for Asthma Management and Prevention. *GINA Report* 2016, <http://www.ginasthma.org/2016-gina-report-global-strategy-for-asthma-management-and-prevention/>. Accessed June 26, 2016.
- [14] Caminati M, Senna G, Guerriero M, et al. Omalizumab for severe allergic asthma in clinical trials and real-life studies: what we know and what we should address. *Pulm Pharmacol Ther*. 2015;31:28–35.
- [15] Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. *Lancet*. 2007;370:185–191.
- [16] Zelko E, Klemenc-Ketis Z, Tusek-Bunc K. Medication adherence in elderly with polypharmacy living at home: a systematic review of existing studies. *Materia Socio-medica*. 2016;28:129–132.
- [17] Asthma, COPD, and Asthma-COPD Overlap Syndrome (ACOS). *GINA Report* 2015, <http://www.ginasthma.org/asthma-copd-and-asthma-copd-overlap-syndrome-acos/>. Accessed June 26, 2016.
- [18] Tat TS, Cilli A. Omalizumab treatment in asthma-COPD overlap syndrome. *J Asthma*. 2016;53:1048–1050.
- [19] Romand P, Kelkel E, Saint-Raymond C, Glas N, Caillaud D, Devouassoux G. Severe uncontrolled asthma in patients over 75 years old: treatment with omalizumab. *Rev Mal Respir*. 2016;33:397–400.
- [20] Korn S, Schumann C, Kropf C, et al. Effectiveness of omalizumab in patients 50 years and older with severe persistent allergic asthma. *Ann Allergy Asthma Immunol*. 2010;105:313–319.
- [21] Long A, Rahmaoui A, Rothman KJ, et al. Incidence of malignancy in patients with moderate-to-severe asthma treated with or without omalizumab. *J Allergy Clin Immunol*. 2014;134:560–567.
- [22] Busse W, Buhl R, Vidaurre CF, et al. Omalizumab and the risk of malignancy: results from a pooled analysis. *J Allergy Clin Immunol*. 2012;129:983–989.