

PHARMACOTHERAPY

Clinical Benefits of 7 Years of Treatment with Omalizumab in Severe Uncontrolled Asthmatics

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Rationale. Severe asthma is characterized by inadequate symptom control and by high rate of inflammation despite high doses of steroids. Omalizumab, a recombinant humanized monoclonal anti-IgE, provides a new therapeutic strategy in severe allergic asthma. **Aims.** This study was aimed to assess whether long-term treatment with omalizumab improved clinical control in severe asthmatics. **Methods.** We investigated omalizumab effects on asthma outcomes evaluating seven severe allergic asthmatic patients who were treated for 7 years with add-on omalizumab. Number of exacerbations, use of antibiotics, additional asthma medications (systemic steroids, nebulized steroids and bronchodilators), and spirometry were analyzed before and after omalizumab treatment. **Results.** Omalizumab was well tolerated by all the studied patients. It improved FEV1 and FEV1/FVC ratio and reduced symptom score, asthma exacerbations, use of antibiotics, and use of nebulized steroids, bronchodilators, and oral corticosteroids. These effects were evident after 4 years of treatment and more pronounced after 7 years of treatment. **Conclusions.** This study underlines the utility of a long-term treatment with omalizumab to improve asthma clinical outcomes in severe asthmatics.

Keywords exacerbations, severe asthma, therapy

INTRODUCTION

Bronchial asthma affects 300 million people worldwide and is predicted to affect an additional 100 million people by 2025. Inadequate control of asthma represents a serious problem despite advances in our understanding of the inflammatory basis of asthma and a growing acceptance of the disease management guidelines (1). Patients with inadequately controlled asthma often have limited therapeutic options and remain at high risk of serious morbidity and mortality (2).

Allergic severe asthma is characterized by increased serum IgE levels. Preventing the allergen-induced release of inflammatory mediators from target cells represents a new strategy in the treatment of atopic diseases (3). The treatment of allergic diseases, including allergic asthma, has been improved by the introduction of omalizumab, a recombinant humanized monoclonal anti-IgE antibody that binds IgE at the same site as the high-affinity IgE receptor and downregulates high-affinity IgE receptors on the surface of circulating basophils and mast cells (4). Omalizumab is effective as add-on therapy in the treatment of patients with persistent severe allergic asthma, reducing the exacerbation rates and improving the quality of life of these patients (5). The demonstrated clinical and functional efficacy of this therapy seems to be linked to the anti-inflammatory activities of this treatment. Omalizumab attenuates both the early-phase

and late-phase responses to inhaled allergens in patients with asthma (6), induces eosinophil apoptosis, and down-regulates IL-2 and IL-13 concentrations in peripheral blood (7).

As the control of inflammation represents the main target of the therapy in severe persistent asthma, it is important to determine the effects of omalizumab on markers of inflammation. A previous study by our group demonstrated that omalizumab increases FEV1 and reduces asthma symptom score and that all these events are correlated to a reduced p-cyclic adenosine mono-phosphate response element binding protein (CREB) (activator of pro-inflammatory events) expression, to an increased Foxp3 (regulation of inflammation) expression, and to a reduced IL-8 (mediator of inflammation associated to frequent exacerbations) expression (8). Till date, only two studies have evaluated clinical changes in severe asthmatics (who had been treated with omalizumab for 6 years) after 1 and 3 years of omalizumab withdrawal, respectively (9, 10). On the basis of these concepts, the general purpose of this study was to assess the number of severe exacerbations, the antibiotic consumption, the systemic corticosteroid bursts, and the add-on nebulized corticosteroid and bronchodilator therapy in a cohort of severe asthmatics treated with omalizumab for 7 years (8).

MATERIAL AND METHODS

Patient Population

The patients included in this study were recruited at the outpatient clinic of the Institute of Biomedicine and Molecular Immunology in Palermo, Italy.

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Seven corticosteroid-dependent asthmatics were defined as previously described (11). These subjects had severe uncontrolled allergic persistent asthma that required a daily dose of inhaled corticosteroids (ICS; 3000 µg of beclomethasone dipropionate equivalent) and long-acting β_2 -agonists (100 µg salmeterol), and inhaled short-acting β_2 -agonists as required. Eligible patients had a baseline IgE > 76 IU/mL, a positive skin prick test, and a positive radioallergosorbent test. They had a FEV1 < 80%, FEV1 reversibility $\geq 12\%$, regularly occurring day or nighttime asthma symptoms, and at least two documented severe exacerbations in the year before starting omalizumab. Severe exacerbations were defined by the presence of symptoms at rest requiring systemic corticosteroids or emergency services or hospitalization. All patients were positive for *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. Patients provided written informed consent before the inclusion in this study. This study was approved by the local ethic committee and was in agreement with the Helsinki Declaration.

Omalizumab treatment was administered for 7 years from 1999 to 2006 (open-label) as part of a prospective clinical trial (CIGE0250011) followed by three extensions promoted by Novartis. Omalizumab was administered subcutaneously every 2 or 4 weeks on the basis of serum IgE levels and of body weight (12).

Clinical Assessment

Scheduled visits (the time interval was compliant to the Novartis clinical trial protocol directions) were planned for all patients to record their clinical history (severe exacerbations, antibiotics, oral corticosteroids, nebulized corticosteroids, and nebulized bronchodilators) and to perform functional evaluations. Pulmonary function tests were performed by the Jaeger Masterlab spirometer (Masterlab E. Jaeger, Wurzburg, Germany). Standard quality control and testing procedures were followed at all examinations (13). We considered the largest FVC and FEV1 from at least five maneuvers. Data are expressed as percentage of the predicted value. Nighttime and daytime asthma symptoms were rated (8) on a 4-point scale: 0 = none; 1 = mild (awareness of asthma symptoms that were easily tolerated); 2 = moderate (asthma symptoms with some discomfort, causing some interference to sleep or daily activities); 3 = severe (incapacitating asthma symptoms, with inability to sleep or perform daily activities). Free serum IgE levels were evaluated at the baseline (before starting omalizumab therapy) and after 7 years of treatment. The median of all the spirometric values obtained for each patient during the year before the treatment, during the fourth year, and during the seventh year of treatment were considered.

Statistics

Data are expressed as mean counts $\pm$ standard deviation. Paired comparisons were performed using the non-parametric method Wilcoxon paired test for comparing, in the same patient, clinical and functional parameters

TABLE 1.—Demographic characteristics.

	Baseline (T = 0)	After 7 years of omalizumab therapy	P-value
Age	50 $\pm$ 8	—	
Gender	3F/4M	—	
Skin prick test positivity	Der Pt/Der Farinae	Der Pt/Der Farinae	
Total IgE (IU/mL)	268 $\pm$ 111	265 $\pm$ 112	n.s.
Free IgE (IU/mL)	268 $\pm$ 111	14.5 $\pm$ 8	<.02
FEV1 (% of predicted—mean $\pm$ SD)	53 $\pm$ 11	71 $\pm$ 12	<.05
FEV1 post-bronchodilator (% of variation)	17 $\pm$ 5	—	
FEV1/FVC ratio (% of predicted—mean $\pm$ SD)	52 $\pm$ 8.7	65 $\pm$ 11	<.05
Symptom score	2.5 $\pm$ 0.4	0.3 $\pm$ 0.2	<.02

before and after omalizumab therapy. *P*-value < .05 was accepted as statistically significant.

RESULTS

Demographic Characteristics of the Subjects

The demographic characteristics, and the clinical and functional evaluations of the studied patients at baseline and after 7 years of treatment with omalizumab are shown in Table 1. The treatment was well tolerated and no relevant side effects or adverse events were recorded. In particular, the recruited patients did not experience any of the most frequent adverse events (lower respiratory tract infections, nasopharyngitis, headache, and sinusitis) (12).

After 7 years of treatment, omalizumab increased FEV1 and FEV1/FVC ratio whereas it reduced the symptom score and the serum IgE levels (Table 1, Figure 1 A and B). The effect on serum IgE after 7 years was similar to that observed after 4 years of treatment (data not shown). The FEV1 increase was present after 4 and after 7 years of treatment in six out of seven patients (Figure 1).

Effect of Omalizumab on Severe Exacerbations

Although it is well known that omalizumab therapy is able to reduce the number of exacerbations in severe allergic uncontrolled asthmatics (5), it is unknown whether this effect persists or is modified following a long-term treatment period. For this purpose, the number of severe exacerbations per year before and after 4 and 7 years of omalizumab therapy was assessed. Omalizumab is effective in reducing the number of severe exacerbations per year and this effect, present after 4 years of treatment, is more evident after 7 years of treatment (Figure 2 As. Similarly, the percentage of reduction in the exacerbation rate is higher after 7 years of treatment (Figure 2 B).

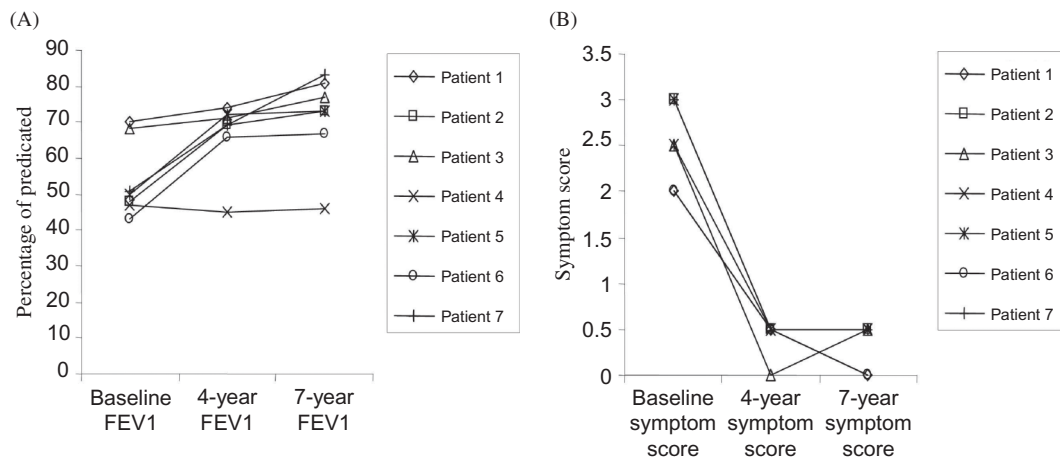


FIGURE 1.—Effect of omalizumab on FEV1 and symptom score. Seven severe asthmatic patients underwent omalizumab as add-on therapy for 7 years. The FEV1 (% of predicted) (A) and symptom score (B) at baseline and after 4 and 7 years of omalizumab treatment were assessed.

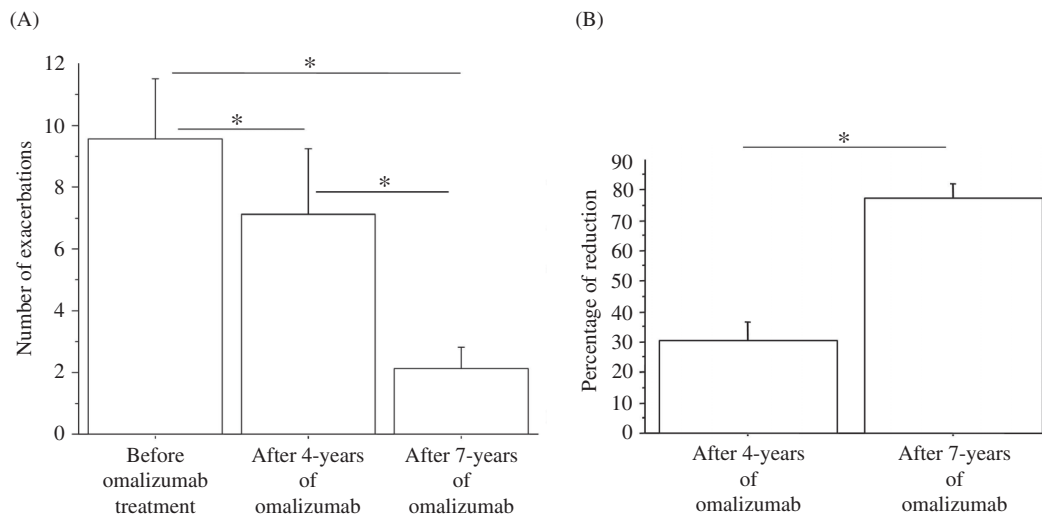


FIGURE 2.—Effect of omalizumab on the number of severe exacerbations. Seven severe asthmatic patients underwent omalizumab as add-on therapy for 7 years. The number of exacerbations at baseline and after 4 and 7 years of omalizumab treatment was assessed. Data are expressed as number of exacerbations/year (mean $\pm$ SD) (A) and as percentage of reduction in the exacerbation rate in comparison to baseline (before therapy) (B). * $p < .05$.

Effect of Omalizumab on the Add-On Therapy for Severe Exacerbations

Add-on therapy with nebulized corticosteroids and bronchodilators, antibiotics, and oral corticosteroids is used to manage a severe exacerbation of asthma. The number of nebulized corticosteroids and bronchodilators cycles, of antibiotic therapy cycles, and of oral corticosteroids cycles per year before and after 4 and 7 years of omalizumab therapy was assessed. Omalizumab is able to reduce the number of nebulized corticosteroids and bronchodilators cycles (Figure 3), the number of antibiotic therapy cycles (Figure 4), and the number of oral corticosteroids cycles (Figure 5). All these effects, present after the first 4 years of treatment, were more evident after 7 years of treatment.

Effect of Omalizumab on the Daily Inhalation Therapy

Finally, we assessed whether the omalizumab long-term therapy was able to modify the need of daily high doses

of ICS plus long-acting inhaled β_2 -agonists. As shown in Figure 6, four patients reduced and two patients discontinued the daily inhalation therapy. Only one patient did not modify the daily inhalation therapy.

DISCUSSION

Asthma is a disease that causes debilitating daily symptoms and unexpected acute exacerbations. Symptoms can seriously limit patients' activities and cause absence from work or school, hospitalization, emergency visits, and a reduced quality of life (14).

Severe persistent asthma causes a substantial morbidity and mortality burden and is frequently inadequately controlled despite intensive guideline-based therapy. The introduction of omalizumab as an add-on therapy for inadequately controlled moderate-to-severe or severe, persistent, allergic asthmatics provided a useful new treatment option for these patients (15).

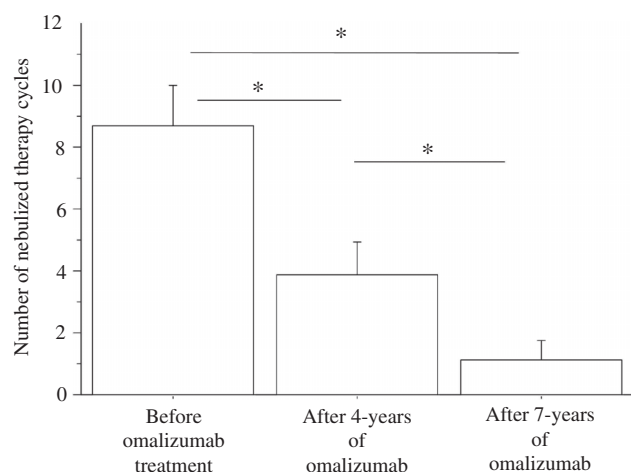


FIGURE 3.—Effect of omalizumab on the use of nebulized corticosteroids and bronchodilators. Seven severe asthmatic patients underwent omalizumab as add-on therapy for 7 years. The cycles of nebulized corticosteroids and bronchodilators at baseline and after 4 and 7 years of omalizumab treatment were assessed. Data are expressed as number of cycles/year (mean ± SD). * $p < .05$.

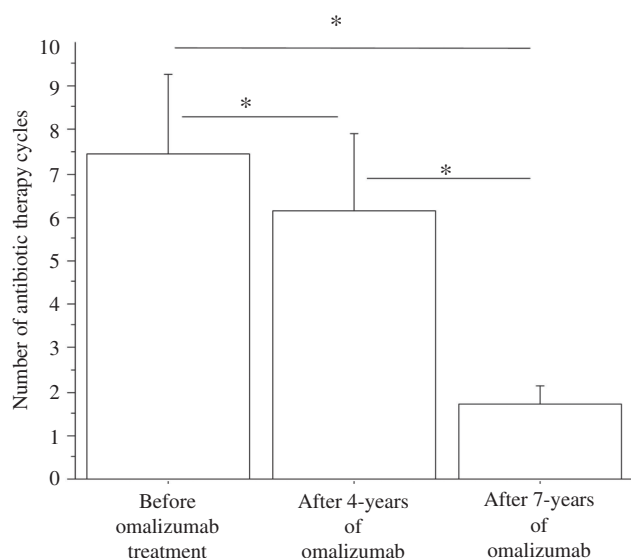


FIGURE 4.—Effect of omalizumab on the use of antibiotics. Seven severe asthmatic patients underwent omalizumab as add-on therapy for 7 years. The number of antibiotic therapy cycles at baseline and after 4 and 7 years of omalizumab treatment was assessed. Data are expressed as number of cycles/year (mean ± SD). * $p < .05$.

Many clinical trials with omalizumab have been reported (16–18), but the treatment period has always been relatively short and after withdrawal the benefit has progressively declined (19). In a comprehensive program of clinical trials, omalizumab has been shown to reduce asthma exacerbation and emergency visit rates and to improve quality of life in patients with severe persistent allergic asthma (5) after 16 and 52 weeks of treatment. Two previous studies by Nopp, performed in severe asthmatics treated for 6 years with omalizumab, evaluated clinical changes after 1 and 3 years of omalizumab withdrawal, respectively (9, 10).

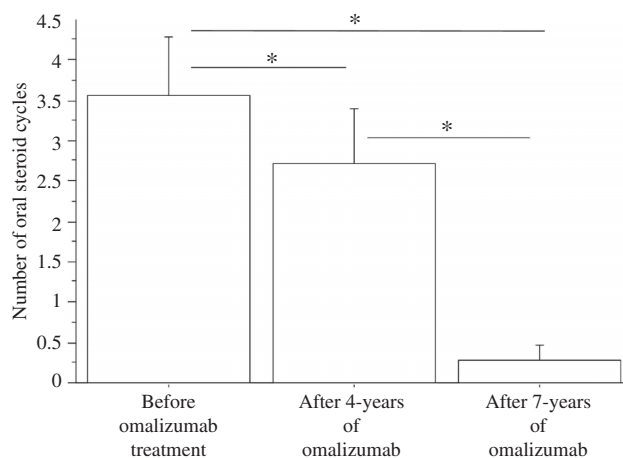


FIGURE 5.—Effect of omalizumab on the use of oral corticosteroids. Seven severe asthmatic patients underwent omalizumab as add-on therapy for 7 years. The number of oral corticosteroid therapy cycles at baseline and after 4 and 7 years of omalizumab treatment was assessed. Data are expressed as number of cycles/year (mean ± SD). * $p < .05$.

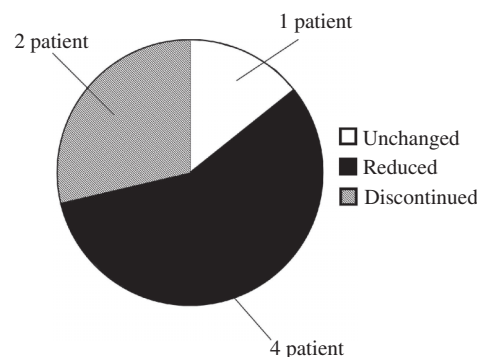


FIGURE 6.—Effect of omalizumab on the daily inhaled therapy. Seven severe asthmatic patients underwent omalizumab as add-on therapy for 7 years. The effect of omalizumab on changing daily inhaled therapy was assessed.

Here, after 7 years of treatment, omalizumab increased FEV1 values and FEV1/FVC ratio and reduced the symptom score, the number of exacerbations, and the add-on asthma therapy with nebulized corticosteroids and bronchodilators, with antibiotics or with oral corticosteroids. All these effects, present during the first 4 years of treatment, were more pronounced during the last 3 years of treatment.

This finding that the use of antibiotics was reduced by omalizumab treatment suggests that infective events could also be better controlled in these severe asthmatics. Asthmatic subjects might also have increased susceptibility to bacterial infections because they have an increased risk of invasive pneumococcal disease, an increased frequency of detection of *Chlamydomphila pneumoniae* in stable asthma, and impaired interferon production in response to lipopolysaccharide (LPS) stimulation (20). Atypical bacterial infections, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, have been associated with asthma exacerbations as well as with chronic asthma (21). Moreover, the reduced use of oral corticosteroids suggests a potential reduced risk of side effects and

comorbidities (diabetes, osteoporosis, and hypertension) in these patients, treated with omalizumab for 7 years. The effectiveness of omalizumab is also confirmed by the finding that the majority of patients reduced and two patients discontinued the daily inhalation therapy with corticosteroids and long-acting β_2 -agonists. In all the recruited patients a significant reduction in exacerbation rate was observed.

Asthma exacerbations consist in a sustained, often progressive, deterioration in asthma symptoms and airflow obstruction that occur over hours to days and can last for days to weeks.

Airway inflammation is a consistent feature of asthma exacerbations where there is evidence of vascular leakage (increased albumin), inflammatory cell infiltration and activation, airway smooth muscle contraction, activation and desquamation of bronchial epithelial cells, and mucus hypersecretion with mucus plug formation (22).

The anti-inflammatory effects of omalizumab may explain the reductions in asthma exacerbations and symptoms seen in our study as well as in other clinical trials in patients with moderate-to-severe or severe, persistent, and inadequately controlled allergic asthma. In these patients, asthma exacerbations are common, account for a significant morbidity, and contribute to generate a high cost of asthma management (22). The optimal strategies for the prevention of asthma exacerbations include the early introduction of anti-inflammatory treatment, most commonly low doses of ICS. In severe uncontrolled asthmatics, the persistence of high rate of inflammation represents a hallmark of the decreased response to corticosteroids. Omalizumab represents in these patients an alternative anti-inflammatory therapy (3).

The interaction between omalizumab and free IgE interrupts a key step in the allergic inflammatory cascade preventing IgE from binding to mast cells, basophils, and dendritic cells, and downregulating IgE receptor expression in these inflammatory cells thereby inhibiting degranulation and the release of inflammatory mediators (4, 23). Omalizumab is able to increase eosinophil apoptosis and to reduce the number of IL-2+ and IL-13+ lymphocytes (24).

A previous study from our group (8) on the same cohort of patients provided compelling evidences that omalizumab treatment is effective in controlling severe uncontrolled asthmatics by modulating mechanisms, crucially involved in the inflammatory processes of the disease. Omalizumab reduces the activation of the pro-inflammatory transcription factor CREB; increases the expression of Foxp3, a transcription factor that promotes T-regulatory activities; and reduces the expression of IL-8 (8). An increased expression of p-CREB in the epithelium and in the sub-mucosa as well as in peripheral blood mononuclear cells (PBMC) and a reduced T-regulatory activity characterize severe uncontrolled asthmatics (25) and might contribute to the increased levels of IL-8 in these patients. IL-8 is a mediator, crucially important in the pathogenesis of asthma (26), and high levels of IL-8 are synthesized from PBMC of severe adult

asthmatics (27) despite these patients receiving ICS therapy (28). Moreover, the IL-8 levels in induced sputum correlate, in moderate asthmatics, with the occurrence of disease exacerbations during a 1-year follow-up period of time (29). The p-CREB/CREB ratio, the Foxp3 expression, and the IL-8 expression, assessed after 7 years of omalizumab treatment and 6 months after discontinuing treatment, correlated with the FEV1 values and the symptom score (8), strongly supporting that the anti-inflammatory effects of omalizumab may explain the reduction of asthma exacerbations and symptoms in these patients.

In conclusion, our study shows that omalizumab treatment is clinically effective over 7 years in a high-risk group of asthmatics and that it is safe as an add-on treatment for uncontrolled severe allergic persistent asthmatics. Omalizumab-treated patients continue to improve between the fourth and the seventh year of treatment.

DECLARATION OF INTEREST

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