

PHARMACOTHERAPY

Omalizumab Reduces Corticosteroid Use in Patients with Severe Allergic Asthma: Real-Life Experience in Israel

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Objective. Approved by the FDA in 2003, omalizumab is the first recombinant humanized monoclonal anti-immunoglobulin E antibody developed for the treatment of allergic asthma. Due to the heterogeneity of asthma symptoms, investigation of the efficacy of omalizumab in patients outside controlled trials is particularly important. The purpose of the current study was to evaluate the efficacy of omalizumab as an add-on treatment for allergic asthma in a real-life setting in Israel. **Methods.** This was a retrospective study based on patient records and computerized database for drug dispensing, emergency room visits, and hospital admissions. **Results.** The sample comprised 33 individuals (18 men, 15 women; mean age 50.0 ± 12.2 , range 25–79) who were treated with omalizumab for severe allergic asthma for a duration of at least 16 weeks. After the initiation of omalizumab therapy, the number of patients who used oral or injected corticosteroids decreased ($p < .003$, .03, respectively), as did the median dosage of oral corticosteroids ($p < .02$). Visits to the emergency room decreased from an incidence of 0.526 visits per person-year to an incidence of 0.246 per person-year ($p < .05$). No adverse reactions to omalizumab were observed. **Conclusion.** Omalizumab as an add-on therapy reduced the use of corticosteroids and improved the control of asthma, as evidenced by reduced asthma-related emergency room visits. This study supports both controlled and uncontrolled studies that have demonstrated the efficacy and safety of omalizumab, and particularly those that demonstrated effectiveness among severe asthma patients. “Real-life” studies are important to identify patients who will most benefit from omalizumab therapy.

Keywords allergy, corticosteroids, hospital admissions, IgE, immunoglobulin E, rhinitis, xolair

INTRODUCTION

Asthma prevalence is increasing in many parts of the world, according to the data recently accumulated from 48 studies (1). This chronic illness affects about 8–10% of the population and causes debilitating symptoms that limit daily activities, reduce quality of life, and lead to life-threatening shortness of breath (2). Severe asthma affects about 10% of patients with asthma and leads to systemic corticosteroid use, recurrent hospital admissions, and increased utilization of health resources (2).

Approximately 90% of asthma is allergic in nature (3). Omalizumab is the first recombinant humanized monoclonal anti-immunoglobulin E (IgE) antibody developed for the treatment of allergic asthma and represents a new paradigm for asthma therapy. Omalizumab was approved by the FDA in June 2003 for the treatment of severe persistent allergic asthma in individuals whose symptoms are inadequately controlled by inhaled corticosteroids. Its efficacy and safety have been demonstrated in several controlled studies (4–13) and, more recently, in non-controlled studies (14–21).

Omalizumab was approved in Israel in 2005 as an add-on treatment for severe persistent allergic asthma, as recommended by the Global Initiative for Asthma

guidelines (22). The Israeli arm of the INNOVATE study showed the addition of omalizumab to standard therapy to reduce by about half asthma exacerbations and asthma-related emergency visits in individuals with allergic asthma (23). The purpose of the current study was to evaluate the efficacy of omalizumab as an add-on treatment for allergic asthma in a real-life setting in Israel.

METHODS

Patients

This is a retrospective study conducted in compliance with the Good Clinical Practice standards and the declaration of Helsinki and approved by the national Ethics Review Board of Clalit Health Services, the largest health maintenance organization in Israel, insuring and servicing 55% of the population of Israel, comprising a population of 3.9 million people. The Ethics Review Board waived the need for informed consent because of the retrospective nature of the study.

We reviewed the medical records of all individuals insured by Clalit Health Services in the northern region of Israel who were treated with omalizumab during the period from January 2008 to December 2009. All were approved for treatment on the basis of severe allergic asthma requiring at least two hospitalizations or two courses of systemic corticosteroid use in the previous year, despite the use of high dosages of inhaled corticosteroids in association with long-acting

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β 2-agonists, total serum IgE of 30–700 IU/ml, and evidence of at least one allergen (by prick test or serum-specific IgE).

Data Collection

Data on the medications related to asthma treatment used by each patient were collected from the Clalit Health Services computerized database for drug dispensing. Medications included omalizumab, inhaled corticosteroids, oral corticosteroids (prednisone, hereafter OCSs), injected corticosteroids (betamethasone dipropionate, hereafter IM BDP), long-acting β 2-agonists, sustained-release theophylline, and leukotriene receptor antagonists. Gender and age were recorded. Outcomes were the number of visits to the emergency room, the number of hospitalizations, and the use of other asthma-related medications. The data were analyzed and compared for two time periods: the year preceding initiation of omalizumab treatment and the year after initiation of treatment.

Statistical Analysis

The McNemar test was used to assess differences in the number of patients treated with omalizumab for at least 16 weeks who used OCS before and after initiating omalizumab treatment. This was repeated for IM BDP and for OCS and IM BDP together. The paired *t*-test was used to examine a change in OCS dose post-treatment. Repeated ANOVA measures were performed to adjust for differences in patient treatment time. Emergency room visits, hospital admissions, and the number of days spent in the hospital were adjusted for the length of observation time by the computation of person-years (incidence per person-year). Paired *t*-tests were then used to assess treatment differences between the two study periods in emergency room incidences, hospital admissions, and days spent in the hospital. Statistical significance was set at $p < .05$.

RESULTS

Thirty-six patients with severe asthma were treated with omalizumab. Three patients who stopped treatment with omalizumab after less than 3 months were not included in the study. Their reasons for treatment cessation were financial and not due to side effects. Thirty-three individuals (18 men, 15 women) were treated at least 16 weeks and met study criteria for analysis (mean age 50.0 ± 12.2 , range 25 to 79).

Mean treatment time was 10.4 months (28.5 person-years or 342 person-months).

The number of patients who used OCS and IM BDP decreased significantly after initiation of omalizumab ($p < .003$, Table 1). In addition, the median dose of OCS decreased significantly ($p < .02$). Visits to the emergency room decreased from 15 in period 1, an incidence of 0.526 visits per person-year, to 7 in period 2, an incidence of 0.246 per person-year ($p < .05$, Figure 1). Hospital

TABLE 1.—Systemic corticosteroids use during the two study periods: the year preceding and the year following initiation of treatment with omalizumab.

Medication	Before	After	<i>p</i> -Values
OCS (oral prednisone)			
Number of patients	28 (84.8%)	19 (57.6%)	<.003
Median dose in mg for patients who used OCS	887.5	1150	NS
Median dose in mg as calculated for the total number of patients (33)	753	662	<.02
IM BDP			
Number of patients	6	1	<.03
OCS and IM BDP	5	2	<.03

Note: NS, not significant.

admissions decreased from 9, an incidence of 0.316 admissions per person-year, to 6, an incidence of 0.210 per person-year ($p > .52$, Figure 1). The number of days spent in the hospital decreased from 32 days, an incidence of 1.123 days per person-year, to 27 days, an incidence of 0.947 days per person-year ($p > .29$).

Responders were identified as those who used less OCS or IM BDP after initiation of treatment with omalizumab, and non-responders as those who used the same amount or more. Of the 33 patients, 20 (60.6%) were classified as responders. Between responders and non-responders, no statistically significant differences were found in age (mean ages: 49.6 ± 13.8 and 50.7 ± 9.7 , respectively, $p > .80$; or gender: 50% and 61.5% males, respectively, $p > .51$).

The medical condition of one patient exacerbated due to gastroesophageal reflux disease (GERD), apparently unrelated to the use of omalizumab; the length of hospital stay was consequently extended. However, excluding this patient from the analysis did not have a significant effect on the overall results: a total of 29 days were spent in the hospital during the pre-treatment period, for an incidence of 1.054 days per person-year, and a total of 8 days during the post-treatment year, for an incidence of 0.291 days per person-year. Nevertheless, this difference was not statistically significant ($p > .39$). There was no significant change between the time periods in the use of inhaled corticosteroids with and without long-acting β -agonist or leukotriene receptor antagonists.

None of our patients had side effects that seemed to associate with the use of omalizumab, except for very mild local reactions as expected from a subcutaneous injection.

DISCUSSION

The main findings of this study are the reduction of systemic corticosteroid use and the reduction in asthma-related emergency department visits subsequent to the initiation of omalizumab as an add-on treatment for severe allergic asthma in a real-life setting. This supports controlled studies that have demonstrated the

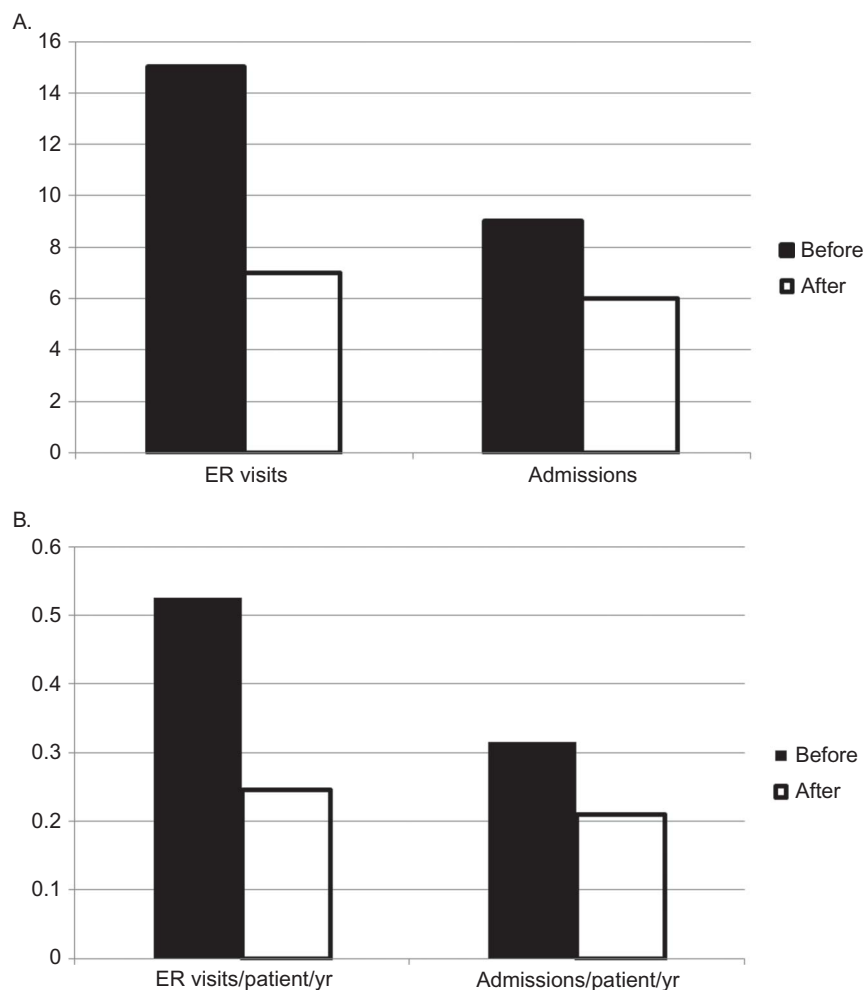


FIGURE 1.—Emergency room visits and hospital admissions during the year before and the year after initiation of treatment with omalizumab. (A) Compared by numbers of events and (B) Compared by number of events per person-year. ER, emergency room; yr, year.

efficacy and safety of omalizumab for the treatment of severe persistent allergic asthma. In addition, more than 50% reduction in emergency visits that we found supports the observational research conducted in France and in Italy that showed decreased emergency room visits; Cazzalo et al. (18) reported an 88% reduction and Molimard et al. (14), a reduction of 65% among those with at least 5-month follow-up. Investigators of the latter emphasized the importance of appropriate dosage and adequate duration to achieve optimal results (14).

Our findings also support studies conducted in France, Germany, and other countries that showed decreased use of steroids subsequent to treatment with omalizumab (17, 21, 24). In the current study, the 61% of patients who decreased the use of systemic corticosteroids subsequent to omalizumab treatment is the same percentage as that reported by a meta-analysis of seven randomized controlled trials (RCTs) (24). Other studies have demonstrated the effectiveness of treatment with omalizumab for persistent allergic asthma, independent of treatment with OCSs (16, 17).

In light of the associations reported between OCSs and cataracts, elevated blood glucose among individuals

without diabetes, osteoporosis, weight gain, acne, and sleep and mood disturbances (25, 26), reduction in the use of OCSs is an important benefit of omalizumab. Nevertheless, abrupt cessation of OCSs can have serious consequences, particularly on the development of eosinophilia or vasculitis (www.pharma.us.novartis.com/product/pi/pdf/xolair).

The current study reflects daily clinical practice in an outpatient setting typical to Israel. The patients were prescribed omalizumab only after approval by an independent committee, based on the severity of their asthmatic condition, according to the strict health regulations in Israel. One quarter of them were treated by oral maintenance corticosteroids. Asthmatic severity would evidently preclude the participation of some of our patients in controlled studies. In contrast, clinical practice investigations enable the inclusion of a diverse population that reflects the heterogeneous nature of asthma and the range of treatments available. Brusselle et al. (15) suggested that the inclusion of more severe patients in the PERSIST study than in controlled trials may explain the greater reduction in exacerbations they observed; omalizumab may be particularly effective for patients with more severe symptoms.

The current study has a number of limitations, particularly due to its retrospective design. Though medication use was assessed by records of pharmacological purchasing, and not by reports of actual use, it is highly likely that patients used the medications that they purchased. Moreover, purchasing rates may overestimate medication used, even further strengthening our conclusion as to the decreased use of corticosteroids subsequent to initiation of omalizumab therapy. In any case, since purchasing data were used for assessment both before and after the start of omalizumab treatment, this should have no effect on the results. The fact that treatment efficacy was not measured by a physiological outcome such as change in FEV is another possible limitation of this study. However, the findings of Wechsler et al. (27) may imply that such outcomes as emergency room visits, which are discernible to patients, may not be less meaningful than physiological outcomes, which did not coincide with subjective perceptions.

In the absence of a control group, an observational study may have the limitation of a selection bias. However, in this study, approval for initiation of treatment with omalizumab by the HMO required strict assessment that patients were most appropriately treated according to GINA guidelines, stage 4, before they were approved to receive omalizumab.

We did not find a statistically significant difference in age between responders and non-responders to omalizumab, as assessed by reductions in OCS use. Also Korn et al. (19) did not find an age-dependent response to omalizumab in their analysis of individuals above and below 50 years of age. The deteriorated disease course of our patient with GERD highlights the importance of identifying demographic and clinical characteristics that may predict positive and negative outcomes to treatment with omalizumab. This is important for both optimal patient selection and effective utilization of health resources. However, analysis of data from seven RCTs did not reveal baseline characteristics that predict response to omalizumab, leading to the conclusion that physician's overall assessment after 16 weeks of treatment appears the most meaningful measure of response to therapy (12).

The high cost of omalizumab is an obstacle to its widespread use. As we reported, three patients were excluded from the current study because they ceased treatment due to financial reasons. Nevertheless, despite the high costs of omalizumab treatment, an analysis based on 49 RCTs recently demonstrated its cost-effectiveness (28).

The mean treatment period in the current study was 10.4 months, with inclusion criterion of 16 weeks, similar to other studies. A double-blind study showed reduced exacerbations of asthma during a 24-week extension to a 28-week study period (7). In another study, Nopp et al. (29) reported that decreased symptoms in 14 of 18 asthma patients were maintained 12–14 months after cessation of omalizumab treatment. More clinical practice studies are needed to determine the optimal duration of

omalizumab as an add-on treatment for patients with different demographic and clinical characteristics and on different treatment regimens.

CONCLUSIONS

This study demonstrated a reduction in the use of corticosteroids and in emergency room visits following therapy with omalizumab in patients with severe symptoms of asthma not adequately treated by other medications. This highlights the importance of identifying the patients who will most benefit from omalizumab and making this therapy accessible to them.

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DECLARATION OF INTEREST

The author reports no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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