

Omalizumab, a recombinant humanized anti-IgE antibody, reduces asthma-related emergency room visits and hospitalizations in patients with allergic asthma

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Background: Prevention of serious asthma exacerbations is an important therapeutic goal in patients with asthma.

Objective: The purpose of this study was to investigate the effect of omalizumab (Xolair), a recombinant humanized monoclonal anti-IgE antibody, on the rate of serious exacerbations during long-term therapy.

Methods: A pooled analysis was completed of 3 multicenter, randomized, double-blind, placebo-controlled phase III studies with omalizumab in adults/adolescents aged ≥ 12 years ($n = 1071$) and in children aged 6 to 12 years ($n = 334$) who required treatment with inhaled corticosteroids for allergic asthma. Rates of serious asthma exacerbations were computed and compared between omalizumab- and placebo-treated patients. Serious exacerbations were those leading to unscheduled outpatient visits, emergency room treatment, or hospitalization during 1 year of treatment.

Results: In all, 767 patients were treated with omalizumab (at least 0.016 mg/kg/IgE [IU/mL], administered subcutaneously every 4 weeks). Another 638 patients were treated with placebo. The rate of unscheduled, asthma-related outpatient visits was lower for the omalizumab-treated patients than for the placebo-treated patients (rate ratio [95% CI], 0.60 [0.44, 0.81]; $P < .01$), as were asthma-related emergency room visits (rate ratio [95% CI], 0.47 [0.24, 1.01]; $P = .05$). Importantly, hospitalizations for asthma were markedly reduced in patients receiving omalizumab (rate ratio [95% CI], 0.08 [0.00, 0.25]; $P < .01$).

Conclusion: Omalizumab reduces the rate of serious asthma exacerbations and the need for unscheduled outpatient visits, emergency room treatment, and hospitalization in patients with moderate-to-severe allergic asthma. (*J Allergy Clin Immunol* 2003;111:87-90.)

Key words: Asthma, allergy, immunoglobulin E, omalizumab, exacerbation, hospitalization

Abbreviation used

RR: Relative risk

Reduction of asthma exacerbations, particularly those episodes requiring emergency room treatment or hospitalization, is an important goal of asthma management.¹ However, despite better pharmacologic treatments and an improved understanding of asthma pathophysiology, many patients continue to have recurrent serious exacerbations. Indeed, in the United States alone there are some 1.5 million emergency room visits and 0.5 million hospitalizations due to asthma exacerbations annually, along with 5000 deaths.² In-patient hospital services represent the largest single direct medical expenditure for this chronic condition, approaching \$2.7 billion in 1994.³

In recent years it has become increasingly recognized that IgE is a crucial mediator of allergic reactions and plays critical roles in the induction and maintenance of chronic airway inflammation and asthma-related symptoms.⁴ Omalizumab, a recombinant humanized monoclonal anti-IgE antibody, represents a novel therapeutic approach to the treatment of allergic asthma.^{5,6} This agent prevents the initiation of the allergic cascade by binding to free IgE. Clinical trials have confirmed that omalizumab effectively controls asthma symptoms while reducing the need for inhaled corticosteroids in adults, adolescents, and children with allergic asthma.⁷⁻⁹

METHODS

Study Design

The aim of the current analysis was to assess the effects of omalizumab on exacerbations of asthma and unscheduled outpatient visits, emergency room treatments, and hospitalizations. We performed a pooled analysis of results from 3 multicenter, randomized, double-blind, placebo-controlled phase III clinical trials of omalizumab (studies 008, 009, and 010).^{7,9} Two studies conducted in adolescents (≥ 12 years old) and adults enrolled 1071 patients^{7,9}; the third study involved 334 children aged 6 through 12 years.⁸ In all studies, each patient (a) had moderate-to-severe allergic asthma of at least 1 year's duration, with a total serum IgE level between 30 and 700 IU/mL (in

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adolescents/adults) or 30-1300 IU/mL (in children), (b) required treatment with daily inhaled corticosteroids, and (c) had a positive skin prick test result to dust mite (*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*), cockroach, dog, or cat.

Each study followed the same design. After an initial baseline period, patients were randomized to receive either omalizumab or placebo administered as a subcutaneous injection every 2 or 4 weeks, dosed according to body weight and baseline IgE (at least 0.016 mg/kg/IgE [IU/mL] every 4 weeks). In the 28-week core study, dosages of inhaled corticosteroid (beclomethasone dipropionate) were kept stable over the initial 16 weeks of treatment (steroid-stable phase) and were then reduced over 8 weeks (25% every 2 weeks), the lowest effective dose being maintained for a further 4 weeks (steroid-reduction phase). Patients were subsequently maintained on their minimum effective beclomethasone dipropionate dose for a further 24 weeks (extension phase) so that the total duration on study treatment was 1 year. Patients in the 2 adolescent/adult studies remained blinded to treatment during the extension phase, whereas the corresponding phase in the pediatric study was open-label therapy, omalizumab being administered to all patients.

Outcome measures and statistical analysis

Rates of asthma-related unscheduled outpatient visits, emergency room treatments, and hospitalizations were estimated by treatment group. A hospitalization was defined as a hospital admission resulting in overnight stay because of asthma exacerbation. Incidence rates were estimated by dividing the total number of events while on study drug by the total number of patient-years at risk on study drug. The number of patient-years at risk was calculated as the amount of time from the first study drug injection to the end of the extension phase. If a patient discontinued prematurely, patient-years and events were accumulated only up to the date of discontinuation. The ratios of incidence rates (omalizumab versus placebo) were computed. Ninety-five percent confidence intervals for rate ratios were computed through use of a bias-corrected bootstrap procedure.¹⁰ *P* values were obtained by inverting the bootstrapped confidence intervals.

Between-group differences for the total number of asthma-related hospitalization days and the mean number of days per asthma-related hospitalization were analyzed through use of the Wilcoxon rank sum test. Hospitalization duration was defined as the amount of time from the earliest admission date to the latest discharge date over all continuous hospital days. Analysis was based on patients' experiencing 1 or more asthma-related hospitalizations during either the core and extension phases (adolescent/adult studies) or the core phase only (pediatric study). If a patient discontinued prematurely, only asthma-related hospitalizations before discontinuation were counted.

RESULTS

Demographics

Overall, 767 patients were randomized to omalizumab and 638 patients to placebo. Patient demographics and baseline characteristics were comparable between the 2 groups in each study.⁷⁻⁹

Asthma exacerbations

As previously reported, significantly fewer omalizumab-treated patients experienced asthma exacerbations (protocol-defined as worsening of asthma control requiring treatment with oral or intravenous corticosteroids or a doubling of the baseline dosage of inhaled corticosteroid). This difference was especially evident for both study phases in the

2 adult/adolescent studies and during the steroid-reduction phase in the pediatric study (Fig 1).⁷⁻⁹ The significant reduction in incidence of asthma exacerbations with omalizumab was maintained during the steroidreduction phase even though there was a concomitant reduction in the use of inhaled corticosteroid therapy compared with placebo.⁷⁻⁹ The effect of omalizumab on exacerbation incidence was maintained over 1 year of treatment.¹¹

Serious exacerbations

In comparison with placebo, 1 year of treatment with omalizumab was associated with a lower incidence of serious asthma exacerbations requiring unscheduled outpatient visits, emergency room treatments, and hospitalizations in adolescents/adults and children (Table I). For all studies combined, 166 unscheduled asthma-related outpatient visits occurred during 779.5 patient-years of follow-up on omalizumab treatment; in comparison, there were 187 outpatient visits during 526.7 patient-years of follow-up on placebo. This equated to 21.30 unscheduled visits per 100 patient-years on omalizumab treatment compared with 35.50 per 100 patient-years on placebo (relative risk [RR] = 0.60; *P* < .01). Similarly, the incidence rate of emergency room treatment for asthma exacerbations was lower for the omalizumab group (omalizumab, 1.80 per 100 patient-years; placebo, 3.80 per 100 patient-years; RR = 0.47; *P* = .05), 14 asthma-related emergency room visits being reported during 779.5 patient-years of follow-up on omalizumab treatment compared with 20 visits during 526.7 patient-years of follow-up on placebo. Similar differences were observed within each of the 3 individual studies.

For all studies combined, 2 asthma-related hospitalizations occurred during 779.5 patient-years of follow-up on omalizumab treatment; this compared with 18 hospitalizations during 526.7 patient-years of follow-up on placebo. The overall incidence rate of asthma-related hospitalization was therefore 92% lower in the omalizumab group than in the placebo group (omalizumab, 0.26 per 100 patient-years; placebo, 3.42 per 100 patient-years; *P* < .01). Similar differences were observed within each individual study. The total number of asthma-related hospitalization days was 4 for patients treated with omalizumab compared with 97 for placebo (*P* < .002). The mean number of days per asthma-related hospitalization for omalizumab-treated patients was less than half that for placebo patients (omalizumab, 2.00; placebo, 5.39; *P* = .152). The effect of omalizumab on asthma-related hospitalizations was consistent across studies and study periods. Further analysis of the hospitalization findings for the subgroup of patients who each reported a similar hospitalization event in the year before study enrollment was precluded by the small number of patients with such a history (omalizumab, *n* = 35 [4.6%]; placebo, *n* = 40 [6.3%]).

DISCUSSION

These findings show that omalizumab reduced the incidence rate of serious asthma exacerbations in adults/ado-

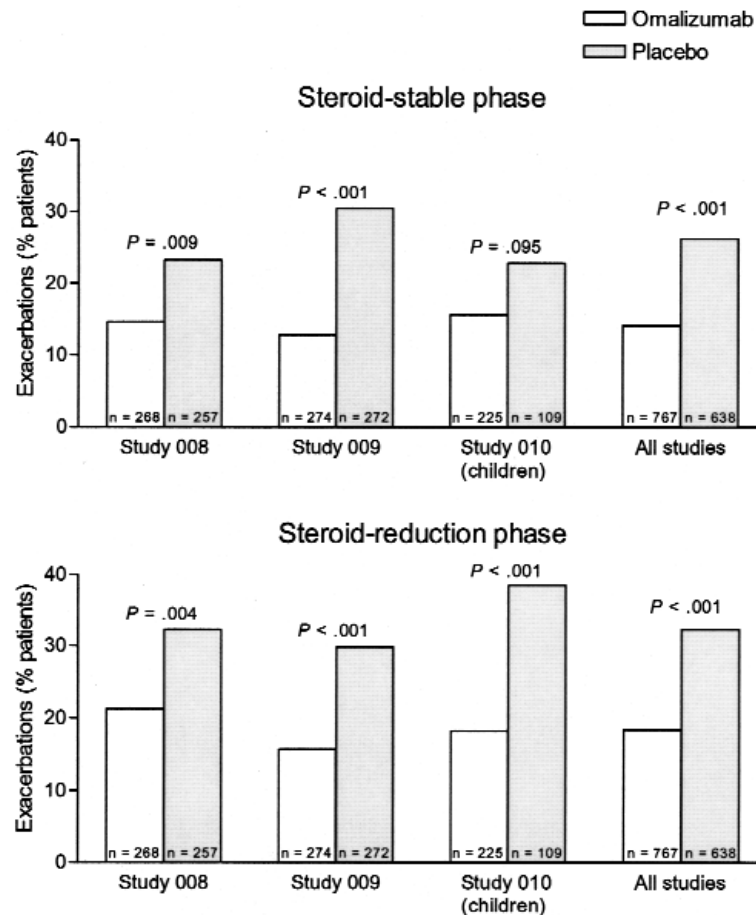


FIG 1. Proportion of patients experiencing asthma exacerbations during the 28-week core study.⁷⁻⁹

TABLE I. Incidence rates of unscheduled outpatient visits, emergency room treatments, and hospitalizations for asthma exacerbations during 1 year of treatment

	Event rate per 100 patient-years (no. of events/total patient-years at risk)		Rate ratio(95% CI)	P value
	Omalizumab	Placebo		
Unscheduled outpatient visits				
Study 008	18.16 (46/253.3)	31.83 (73/229.4)	0.57 (0.35, 0.92)	.02
Study 009	14.84 (39/262.9)	32.07 (77/240.1)	0.46 (0.26, 0.80)	<.01
Study 010 (children)	30.77 (81/263.3)	64.61 (37/57.3)	0.48 (0.28, 0.84)	<.01
All studies	21.30 (166/779.5)	35.50 (187/526.7)	0.60 (0.44, 0.81)	<.01
Emergency room treatment				
Study 008	1.18 (3/253.3)	3.05 (7/229.4)	0.39 (0.00, 1.76)	.17
Study 009	1.14 (3/262.9)	2.92 (7/240.1)	0.39 (0.00, 2.75)	.25
Study 010 (children)	3.04 (8/263.3)	10.48 (6/57.3)	0.29 (0.09, 1.07)	.06
All studies	1.80 (14/779.5)	3.80 (20/526.7)	0.47 (0.24, 1.01)	.05
Hospitalization				
Study 008	0.39 (1/253.3)	1.31 (3/229.4)	0.30 (0.00, +Inf)	.39
Study 009	0.38 (1/262.9)	4.16 (10/240.1)	0.09 (0.00, 0.56)	<.01
Study 010 (children)	0.00 (0/263.3)	8.73 (5/57.3)	0.00 (Undefined)	Undefined
All studies	0.26 (2/779.5)	3.42 (18/526.7)	0.08 (0.00, 0.25)	<.01

lescents and children with allergic asthma requiring treatment with inhaled corticosteroids. The results extend previously reported findings showing that omalizumab reduces the frequency and incidence of asthma exacerbations

while reducing the intake of inhaled corticosteroids in patients with allergic asthma.⁷⁻⁹

Reducing the incidence of serious asthma exacerbations has important implications from the patient's per-

spective: the avoidance of unscheduled outpatient visits, emergency room treatments, or hospitalizations lessens the likelihood of absenteeism from work/school and allows patients to spend more time doing normal activities. This profile can be expected to confer quality-of-life benefits. Moreover, given that hospitalization is a recognized risk factor for fatal asthma,¹² the reduced risk of this outcome with omalizumab therapy suggests that its use might be associated with a reduction in asthma-related mortality. In addition, inasmuch as hospitalization accounts for a significant proportion of the expenditure on asthma treatment,³ the ability of omalizumab to reduce hospitalizations by up to 92% and the average duration of a hospitalization by up to 63% might have a substantial impact on the cost of care in patients with allergic asthma.

Exacerbation rates during the steroid-stable and -reduction phases of the study were similar within each treatment group (Fig 1), which argues against steroid tapering as a possible cause of exacerbation in some patients. This assumption is supported by an overall analysis of the cited reasons for exacerbation. Indeed, data for all randomized patients for the combined steroid-stable and -reduction phases show that viral and upper respiratory infections (including pharyngitis, colds, and influenza) were the most frequently reported reasons for asthma exacerbation, in accordance with previous studies.^{13,14} Interestingly, recent findings indicate that the atopic status of patients recruited to the present study might be associated with a predisposition to a more severe asthmatic response to viral respiratory infection, especially when concomitant allergen exposure is high.¹⁵

In conclusion, by helping to control symptoms in patients with allergic asthma, omalizumab might reduce the incidence of serious, potentially life-threatening asthma exacerbations during long-term therapy. This profile can be expected to have significant benefits from the patient's perspective and might prove to reduce the overall cost of care.

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