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REVIEW ARTICLE

Response of Older Patients with IgE-Mediated Asthma to Omalizumab: A Pooled Analysis

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Asthma in older adults is under-recognized and possibly associated with allergic triggers. We conducted a pooled analysis of omalizumab double-blind, placebo-controlled trials to evaluate efficacy in older adults. Data for the total study population and subjects aged ≥ 50 years with moderate-severe allergic asthma were examined. We used Poisson regression to analyze the number of asthma exacerbations and logistic regression to evaluate treatment effectiveness. Symptom scores and total rescue medication puffs were evaluated by analysis of covariance. Omalizumab reduced the risk of clinically significant asthma exacerbations, led to a significantly greater response in patient/investigator-reported global effectiveness, improved asthma symptom scores, and reduced rescue medication use in adults ≥ 50 years with moderate-severe allergic asthma.

Keywords adult, asthma, IgE, older, omalizumab

INTRODUCTION

Asthma in the elderly is now recognized to be more prevalent than previously appreciated. Reported rates of asthma prevalence in Americans 65 years of age and older range from 3.8% for men and 7.1% for women (1). In 1999, Enright et al. reported an asthma prevalence of 4% in this same age group, noting that a significant proportion of these patients had received alternate diagnoses to explain asthma symptoms, suggesting under-diagnosis (2). The self-reported rate of asthma in the middle-aged population is 4.6%, and the annual number of asthma episodes or attacks reported in this age group from 1997–1999 is almost 3.5 million per year (3). The Centers for Disease Control (CDC) now recommends annual influenza vaccination for individuals ≥ 50 years of age, especially those with respiratory diseases including asthma (4), highlighting the importance of disease management in these older asthmatics at higher risk for influenza-related respiratory complications. Under-treatment of asthma in older adults is now well recognized (2,5,6) as is the observation that adherence to guideline therapy may reduce the morbidity and mortality associated with the condition in this population (7). The overall asthma burden may increase over time with the increase in the proportion of older adults in the total population.

Atopic disease has been considered to be less common in the elderly, in whom a decline in serum total IgE levels was observed (8, 9). However, some recent data indicate a substantial prevalence of allergen-sensitization (10),

without significant age-related decline in skin test reactivity (9, 11, 12) or in mean serum immunoglobulin E (IgE) levels (11) in elderly asthmatics, supporting the notion that IgE-dependent disease mechanisms remain relevant in this group. In elderly asthmatics with moderate to severe persistent disease, 60% had skin test positivity and 74.7% had serologic evidence of sensitization to at least one indoor allergen (10, 12). Burrows et al. reported a linear association with IgE levels and the risk of asthma, noting that the relationship remained linear even in the elderly (8). Omalizumab (OMA), a humanized monoclonal immunoglobulin E (IgE) antibody, binds to the C ϵ 3 domain of IgE, forming complexes that prevent IgE from binding to the high-affinity (Fc ϵ RI) receptors on mast cells and basophils. This impedes the process leading to cellular degranulation and release of inflammatory mediators and limits the allergic inflammatory cascade. OMA has been shown to attenuate early- and late-phase asthmatic responses (13, 14) and has demonstrated anti-inflammatory effects on the airways of asthmatics (15) and improvements in asthma-related quality of life (16, 17).

While OMA has been shown to be effective in reducing asthma exacerbations, reducing inhaled corticosteroid (ICS) requirements and improving asthma symptom scores in patients with allergic asthma who remain uncontrolled on ICS (18–20), reports of its efficacy have not focused specifically on the older patient population. The impact of asthma is greater in this age demographic than in younger patients as manifested by greater severity of lung function impairment (21, 22), greater hospitalization risk (23), reduced quality-of-life scores (12), and increased mortality (24).

We undertook a subgroup analysis of patients 50 years of age and older from a pooled database of efficacy trials in asthma to assess treatment response to OMA and patient-reported and investigator-reported treatment effectiveness. We also analyzed asthma symptom scores, as well as safety and tolerability of OMA in this age group.

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TABLE 1.—Summary of studies with common inclusion and exclusion criteria.

	Study 1 (Busse, 18)	Study 2 (Solèr, 19)	Study 3 (Holgate, 20)	Study 4 (Humbert, 25)	Study 5 (Vignola, 26)
Inclusion criteria:					
Asthma ≥ 1 yr	Y ^a	Y	Y	Y	Y
Asthma severity	Severe	Moderate to severe	Severe	Severe	Moderate to severe
IgE levels (IU/mL)	30–700	30–700	30–700	30–700	30–1,300
(+) skin prick test	Y	Y	Y	Y	Y
FEV ₁ (% predicted)	40–80	40–80	40–80	40–80	40–80 (GINA 2002 guidelines)
FEV ₁ reversibility $\geq 12\%$	Y	Y	Y	Y	Y
Concomitant medications:					
i. LABA ^b	N ^a	N	Y	Y	Y
ii. theophyllines	N	N	N	Y	N
iii. LTRA ^c	N	N	N	Y	N
Exclusion criteria:					
Prior exposure or sensitivity to OMA	Y	Y	Y	Y	Y
Acute URI ≤ 4 weeks before screening	Y	Y	Y	NS ^a	Y
Elevated IgE for reasons other than atopy	Y	Y	Y	Y	Y
Oral corticosteroids	Y	Y	N	N	Y

^aY = yes, N = no, NS = not stated.^bLABA = long-acting beta agonist.^cLTRA = leukotriene receptor antagonist.

METHODS

Study Design

The five studies included in this analysis represented the total of randomized, double-blind, placebo-controlled efficacy trials performed as part of the clinical research program supporting registration of OMA (18–20, 25, 26). The studies were similar in design and in efficacy variables, which allowed for use of patient-level data for a precise estimate of effects in this pooled analysis. Patients with asthma that was either moderate or severe based on National Heart, Lung, and Blood Institute (NHLBI) guidelines (27) or Global Initiative for Asthma (GINA) (28) classification were enrolled. Allergic sensitization to at least one perennial aeroallergen was confirmed on the basis of skin test reactivity or by radioallergosorbent (RAST) testing. Other inclusion criteria included at least a 1-year history of asthma, IgE levels between 30 and 700 International Units (IU)/mL (up to 1300 IU/mL was allowed in one study), a forced expiratory volume in 1 second (FEV₁) 40% to 80% of predicted, FEV₁ reversibility of $\geq 12\%$, and at least a moderate dose of inhaled corticosteroids. Study criteria excluded patients who had previously received or demonstrated sensitivity to OMA, had an acute respiratory tract infection within 4 weeks of study entry, had IgE elevation for reasons other than atopy, or required doses of OMA more than 750 mg per month (maximal dosage allowed based on dosing tables used in each study). Long-acting beta-2 agonists were allowed in three studies provided that use was established before randomization (20, 25, 26). One study allowed use of additional asthma controllers such as theophyllines, oral beta-2 agonists, leukotriene receptor antagonists, and maintenance oral corticosteroids (25), provided that use was established before randomization.

OMA was administered every 2 to 4 weeks, at a dose based on body weight and serum total IgE level, to provide a total monthly dose of 0.016 mg/kg/IU (IgE/mL). Four (18, 19, 25, 26) of the five studies were of 28 weeks duration, and one study (20) was 32 weeks duration. Standard asthma management was allowed in each study. The number of asthma exacerbations was the primary efficacy variable in four of the

studies. In the remaining study (20), the number of asthma exacerbations was recorded as a secondary efficacy variable, with the primary efficacy variable defined as the percentage reduction from baseline of fluticasone dose over the study duration. Table 1 summarizes the major points of each study's inclusion and exclusion criteria.

Patients recruited for the studies were part of multicenter, international clinical trials performed in 25 countries in North, Central and South America, Europe, Australia, and Africa. All patients provided informed written consent, and protocols were approved by the respective institutional review boards.

Asthma Exacerbations

Clinically significant asthma exacerbations were defined in all studies as a worsening of asthma symptoms requiring treatment with systemic corticosteroids (18–20, 25, 26); three of the five studies also defined an exacerbation as a worsening of asthma symptoms necessitating doubling of the baseline ICS dose (18, 19, 26). For patients who discontinued prematurely, events were imputed as described previously (18–20, 25, 26).

Other Outcome Measures

In four studies, patients recorded daytime and nocturnal asthma symptom scores on daily diary cards (5-point scale, with 0 indicating an absence of symptoms, and 4 indicating symptoms limiting routine activity in the daytime or sleep at night despite the use of rescue medication) as well as the presence (= 1) or absence (= 0) of morning symptoms, which were summed for a maximum score of 9. The total daily symptom score has been validated as a means to measure the efficacy of asthma treatment (29). Study 5 was not included in this symptom score analysis since it used a different scoring tool (26). The change from baseline in use of beta-2 agonist rescue medication was compared between treatment and placebo groups in each of the studies. Global evaluation of treatment effectiveness (GETE) rating was performed by study patients and investigators evaluating patients during the studies, all of whom remained blinded to treatment

assignment. Quality of life was assessed via self-administered Juniper's Asthma Quality of Life Questionnaires (AQLQ).

Statistical Analysis

The safety population included all randomized patients who received at least one dose of study medication. The intent-to-treat population included all randomized patients and was used for efficacy analyses (18–20, 25, 26).

The number of clinically significant asthma exacerbations was analyzed using a Poisson regression model (30). A logistic regression model was used to analyze the patient GETE (PGETE) and investigator GETE (IGETE) (31).

Analysis of covariance (ANCOVA) was used to analyze the change from baseline in mean asthma symptom scores and mean number of puffs of rescue beta-2 agonist; least-squares mean (LSM) differences and 95% confidence intervals (CI) between treatment groups were calculated based on the ANCOVA model. Explanatory variables used in the models are identified in the footnotes of Tables 4, 5, 7, and 8. ANCOVA was also used to analyze the change from baseline and percent change from baseline in AQLQ scores; explanatory variables used in this model included age, gender, history of depression, study, treatment, and baseline scores.

The analysis of the data for the older subgroup paralleled the approach taken for the overall pooled population for all variables above.

Statistical analyses were performed using SAS, version 8.2.

RESULTS

Baseline Study Population Characteristics

The pooled population comprised 2,236 patients, of whom 1,136 received OMA and 1,100 received placebo. Baseline demographics and background characteristics are shown in Table 2. The mean age of the overall pooled population was 40 years; there was a greater proportion of females. The mean baseline IgE level was 211 IU/mL. Mean baseline percent predicted FEV₁ was 69.6%. The majority of patients (72%) had moderate to severe asthma based on percent predicted FEV₁. Baseline mean daily ICS dose was similar in treatment and placebo groups [1400 micrograms (mcg) beclomethasone (BDP)-equivalent].

The subgroup of patients 50 years and older consisted of 601 patients, of whom 296 received OMA and 305 received placebo. The mean age of this subgroup was 58 years; the ma-

jority were women. Mean baseline IgE level was 184 IU/mL, and mean baseline percent predicted FEV₁ was 64.6%. Eighty percent of patients in the older subgroup had moderate to severe asthma. Baseline mean daily ICS dose was equivalent to approximately 1600 µg of BDP for this subgroup (Table 2).

Patient Disposition

In the overall population, 214 patients discontinued treatment, of whom 89 were receiving OMA and 125 were receiving placebo. Twenty-nine patients (1.3%) discontinued for adverse events and 34 patients (1.5%) discontinued for unsatisfactory therapeutic effect. In the older subgroup, 48 patients discontinued treatment, 14 in the OMA group and 34 in the placebo group. Similar to the overall population, 1.5% (9 patients), and 1.8% (11 patients) discontinued for adverse events and unsatisfactory treatment effect, respectively, all of the latter occurring in the placebo-treated group. See Figures 1 and 2 for disposition data.

Efficacy

Asthma Exacerbations. Relative risks (RR) of clinically significant asthma exacerbations (OMA relative to placebo) based on Poisson regression for the individual studies as well as the pooled analysis are reported in Table 3, for both the overall population and the older subgroup. In all but one of these studies (20), the RR for OMA versus placebo for the number of exacerbations was lower in both the total population and the older subgroup. Study 3 had the smallest number of patients and the greatest variability about the point estimate of RR of exacerbation. The mean number of asthma exacerbations in the overall population was 0.74 for OMA versus 1.07 for placebo; corresponding values for the older subgroup were 0.66 and 1.14, respectively. The RR of asthma exacerbations for the overall population was 0.78 (95% CI: 0.62, 0.97); for the older subgroup the RR was similar: 0.72 (95% CI: 0.48, 1.09). The RR for each of the evaluated studies, the overall population, and the ≥50 year subgroup are represented graphically in Figure 3. If one includes only the four trials where the primary efficacy variable was the number of exacerbations (18,19,25,26), the point estimates for the RR of clinically significant asthma exacerbation were 0.63 (95% CI: 0.53, 0.75) for the overall population and 0.58 (95% CI: 0.42, 0.80) for the older subgroup; however, the present analysis includes all five trials.

TABLE 2.—Baseline demographics.

Treatment assignment	Pooled			≥50 years subgroup		
	Omaliuzumab	Placebo	Total	Omaliuzumab	Placebo	Total
Number (%)	1,136 (51)	1,100 (49)	2,236	296 (49)	305 (51)	601
Sex [n (%)]:						
Female	660 (58)	642 (58)	1,302 (58)	172 (58)	192 (63)	364 (61)
Male	476 (42)	458 (42)	934 (42)	124 (42)	113 (37)	237 (39)
Mean age (years)	40.5	40.2	40.3	58.6	57.3	58.0
Mean asthma duration (years)	21	21		26	27	
Baseline mean IgE (IU/mL)	213	210	211	190	178	184
Baseline FEV ₁ (L)	2.36	2.42		1.83	1.90	
Baseline % pred FEV ₁	69	70	69.6	64	65	64.6
Baseline ICS dosage (in BDP-equivalent µg/day)	1409	1402	1406	1609	1606	1608
Baseline mean total Asthma symptom score (SD)	3.45 (1.8)	3.47 (1.8)		3.35 (1.9)	3.40 (1.8)	
Baseline mean total rescue medication puffs (SD)	4.45 (4.9)	4.26 (4.8)		4.48 (4.4)	4.37 (4.4)	

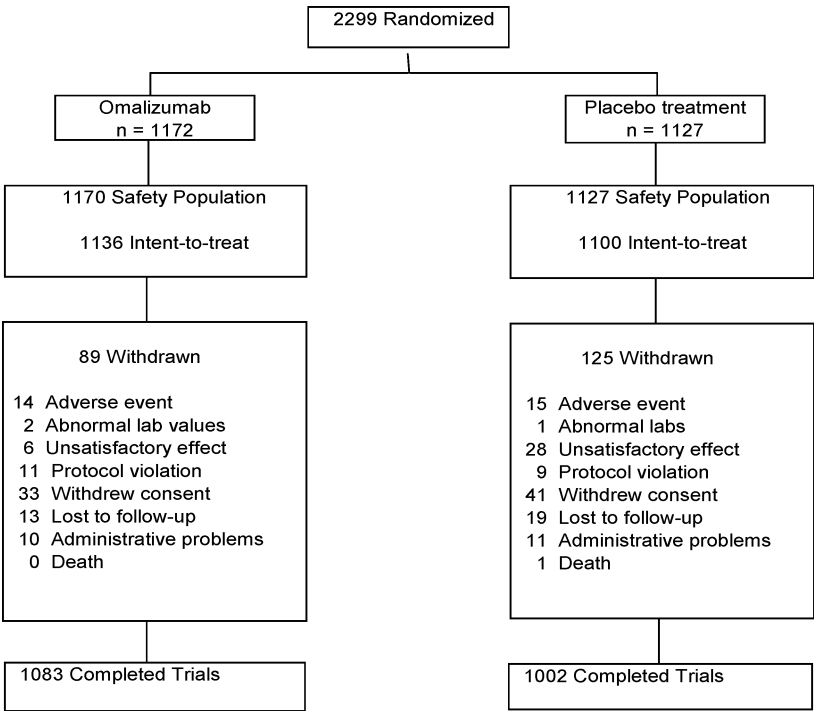


FIGURE 1.—Patient disposition (overall study population).

Mean Asthma Symptom Scores. Treatment with OMA resulted in significant improvement in mean asthma symptom scores as compared with placebo in the overall population (mean change from baseline: -1.00 vs. -0.59 ; LSM differ-

ence -0.40 ; 95 % CI: -0.53 , -0.28 ; $p < 0.0001$), and a similar reduction in symptom scores was shown in the 50-year or older subgroup (-0.86 vs. -0.59 ; LSM difference -0.26 ; 95% CI: -0.51 , -0.01 ; $p = 0.0411$). Improvements

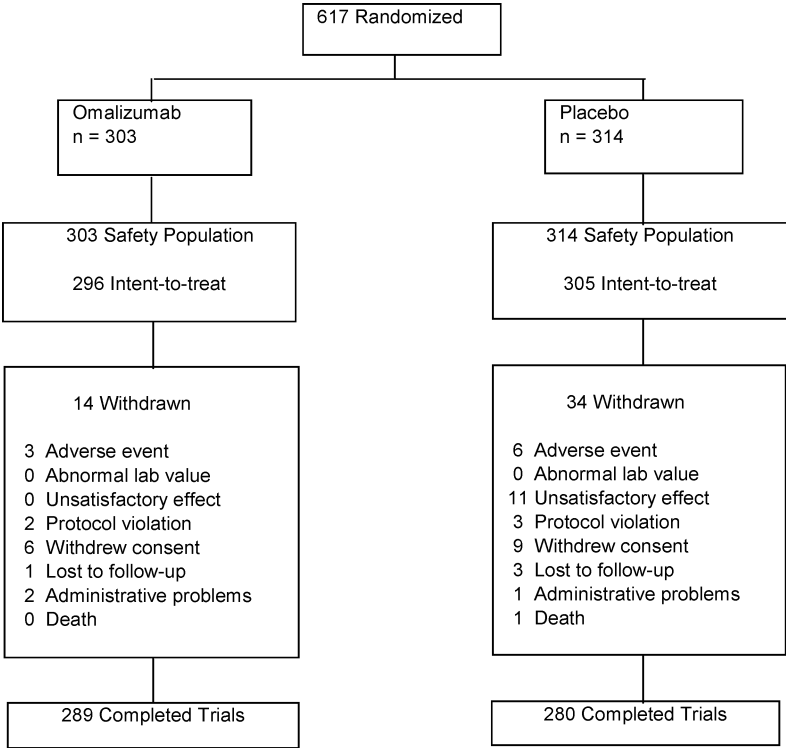


FIGURE 2.—Patient disposition (≥ 50 -year olds subgroup).

TABLE 3.—Relative risks and corresponding 95% confidence intervals (omalizumab relative to placebo) for the overall population and the subgroup of subjects aged 50 years or older.

	Study 1 ^a	Study 2 ^a	Study 3 ^a	Study 4 ^b	Study 5 ^b	Pooled ^c
Overall	<i>N</i> = 496 0.61 (0.43, 0.87)	<i>N</i> = 512 0.49 (0.34, 0.72)	<i>N</i> = 341 1.22 (0.69, 2.15)	<i>N</i> = 419 0.79 (0.58, 1.06)	<i>N</i> = 394 0.66 (0.43, 1.00)	<i>N</i> = 2162 0.78 (0.62, 0.97)
≥50 yrs	<i>N</i> = 99 0.49 (0.25, 0.97)	<i>N</i> = 138 0.71 (0.39, 1.29)	<i>N</i> = 120 1.11 (0.40, 3.10)	<i>N</i> = 140 0.63 (0.37, 1.06)	<i>N</i> = 89 0.47 (0.19, 1.15)	<i>N</i> = 586 0.72 (0.48, 1.09)

^aPoisson regression model with the outcome of (imputed) exacerbations that includes the explanatory variables of treatment group, sex, and baseline IgE.

^bPoisson regression model with the outcome of (imputed) exacerbations that includes the explanatory variables of treatment group, sex, baseline IgE, and history of exacerbations.

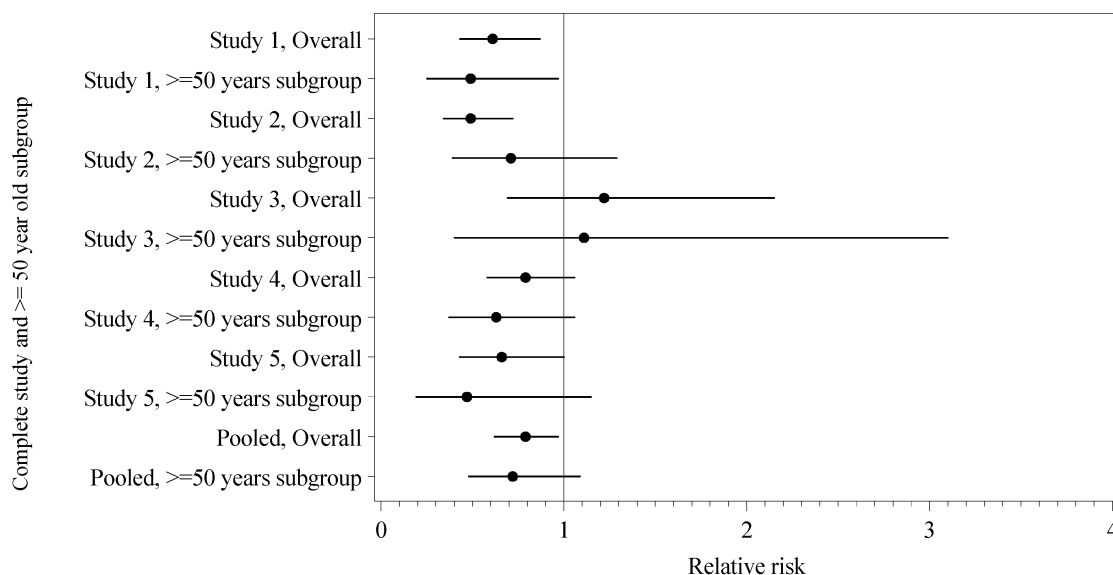
^cPoisson regression model with the outcome of (imputed) exacerbations that includes the explanatory variables of treatment group, sex, baseline IgE, history of exacerbations, and study.

with OMA were observed for both the overall population and the older subgroup by week 4 (Tables 4 and 5) and were consistent over the remainder of the treatment periods.

GETE Scores. Patients who received OMA were more likely to rate their treatment effectiveness as good or excellent (OMA: 64.2% [*n* = 729]; placebo: 43.9% [*n* = 483]). This result was maintained in the older subgroup (OMA: 64.9% [*n* = 192]; placebo: 43.3% [*n* = 132]). Investigators rated patient response to treatment as good or excellent in 58.5% (*n* = 665) of those on OMA, and 36.9% (*n* = 406) of those on placebo in the overall population. The corresponding values for the over-50 subgroup were consistent with the effect reported for the overall population (OMA: 56.1% [*n* = 166]; placebo: 36.7% [*n* = 112]). Odds ratios were calculated using logistic regression analysis (Table 6). For the overall population the odds of treatment effectiveness

as assessed using IGETE (good or excellent) for OMA versus placebo was 2.58 (95% CI: 2.16, 3.08); in the older subgroup it was 2.21 (95% CI: 1.57, 3.12). The respective odds ratios for a good or excellent rating based on PGETE were 2.46 (95% CI: 2.06, 2.95) and 2.53 (95% CI: 1.79, 3.58).

Mean Beta-Agonist Use. Overall usage of beta-2 agonists was low, and all groups recorded reductions in use. There was a 62% and 42% greater reduction in mean number of albuterol puffs from baseline (OMA vs. placebo) in the overall population and the older subgroup, respectively. The LSM change from baseline in total rescue puffs over time in the overall population was −0.96 for OMA vs. −0.38 for placebo (LSM difference −0.58, 95% CI: −0.80, −0.37; *p* < 0.0001). The mean change from baseline in the over-50 subgroup was −0.78 for OMA and −0.31 for placebo (LSM difference −0.47, 95% CI: −0.92, −0.02; *p* = 0.0414) (Tables 7 and 8).



Poisson regression models for Studies 1, 2, and 3 include treatment group, sex, and baseline IgE as explanatory variables. Poisson regression models for Studies 4 and 5 include treatment group, sex, baseline IgE, and history of exacerbations as explanatory variables. The Poisson regression model for the pooled analysis includes treatment group, sex, baseline IgE, history of exacerbations, and study as explanatory variables.

FIGURE 3.—Relative risks (OMA relative to PBO) for number of exacerbations by study, overall population, and the subgroup 50 years of age or older.

TABLE 4.—Analysis of the change from baseline in mean total asthma symptom score over time in the overall population.

Period	Omalizumab		Placebo		Omalizumab vs. Placebo		
	N	LSM	N	LSM	LSM difference	95% CI	p value ^a
0–4 weeks	876	−0.50	858	−0.28	−0.22	(−0.32, −0.12)	<0.0001
>4–8 weeks	860	−0.81	831	−0.43	−0.38	(−0.50, −0.26)	
>8–12 weeks	847	−0.94	815	−0.57	−0.37	(−0.50, −0.24)	
>12–16 weeks	832	−1.03	789	−0.60	−0.43	(−0.56, −0.30)	
>16–20 weeks	805	−1.04	763	−0.64	−0.40	(−0.53, −0.26)	
>20–24 weeks	795	−1.16	746	−0.71	−0.45	(−0.59, −0.31)	
>24–28 weeks	778	−1.25	733	−0.78	−0.48	(−0.62, −0.34)	
>28–32 weeks ^b	157	−0.45	145	−0.07	−0.38	(−0.64, −0.13)	
End of study ^c	880	−1.00	861	−0.59	−0.40	(−0.53, −0.28)	

LSM = least-squares mean.
Note: Studies 1, 2, 4, and 5 are randomized 28 week double-blind placebo-controlled omalizumab studies in moderate to severe asthma patients. Study 3 is a randomized 32-week double-blind placebo-controlled omalizumab study in severe asthma patients. Study 5 was not included in the analysis.
Note: The total asthma symptom score was defined as the sum of the morning asthma score, daytime asthma score, and nocturnal asthma score. The mean total asthma symptom score per day for each patient for a given period was calculated by summing the morning, daytime, and nocturnal scores in a day for that period and dividing by the number of days.
^aBased on analysis of covariance model with treatment, country, dosing schedule, and baseline, mean total asthma symptom score as explanatory variables. Least-Square mean differences based on the model were calculated between treatment groups and 95% confidence intervals were constructed.
^bApplicable to study 3 only.
^cEnd of study for studies 4 and 5 was defined as the end of the 28-week double-blind period. End of study for studies 1, 2, and 3 was defined as the last observation in the double-blind stabilization phase.

Quality of Life. Total AQLQ score and scores in the four domains assessed (activity limitations, symptoms, emotional function and exposure to environmental stimuli) significantly improved in the overall population for OMA, with LSM score changes between 0.92 and 0.97 (placebo 0.57 to 0.64). The respective LSM for percent change from baseline scores ranged from 25% to 30% for those receiving OMA and 17% to 22% for placebo. The older subgroup exhibited a percent change from baseline improvement in AQLQ scores of 15% to 20% for those receiving OMA (13% to 20% placebo), the same direction and magnitude of change as for the overall population.

General Safety. The incidence of serious adverse events (SAE) was similar between OMA and placebo groups in the overall population (3.2% and 3.0%, respectively), as well as for the over-50 subgroup (4.6% and 4.5%, respectively). The proportion of adverse events leading to study drug discontinuation in the overall population was 1.2% (1.0% OMA, 1.4% placebo), which was similar to the results for the older sub-

group (1.6%: <1% OMA, 2.2% placebo). Adverse events that were believed to be related to study drug occurred in approximately 7.7% of the overall population (8.5% OMA, 6.9% placebo) and to a similar degree in the older subgroup (9.9% OMA, 7.0% placebo).

DISCUSSION

This analysis of response demonstrated that OMA exhibited efficacy in older patients that was similar to that experienced by the general study population. OMA reduced the risk of asthma exacerbations in older patients, with the RR falling within the confidence interval of the overall population. The results also support the concept that IgE-mediated mechanisms play an important role in asthma in the elderly. Data from a recent analysis of serologic markers to common inhaled antigens in a group of middle-aged men identified an increase in atopy in this group over the past quarter century, reinforcing the important role of IgE in older individuals (32). In our analysis, baseline IgE levels in the older subgroup were

TABLE 5.—Analysis of the change from baseline in mean total asthma symptom score over time in the ≥50 years of age subgroup.

Period	Omalizumab		Placebo		Omalizumab vs. Placebo		
	N	LSM	N	LSM	LSM difference	95% CI	p value ^a
0–4 weeks	239	−0.42	244	−0.22	−0.20	(−0.38, −0.01)	0.0411
> 4–8 weeks	236	−0.66	233	−0.42	−0.24	(−0.47, −0.01)	
> 8–12 weeks	235	−0.84	231	−0.65	−0.19	(−0.45, 0.06)	
> 12–16 weeks	233	−0.90	225	−0.66	−0.23	(−0.49, 0.02)	
> 16–20 weeks	227	−0.85	217	−0.71	−0.14	(−0.41, 0.12)	
> 20–24 weeks	224	−0.96	212	−0.67	−0.29	(−0.56, −0.03)	
> 24–28 weeks	222	−0.99	208	−0.71	−0.28	(−0.57, 0.00)	
> 28–32 weeks ^b	59	−0.39	48	0.14	−0.53	(−1.07, 0.00)	
End of study ^c	240	−0.86	244	−0.59	−0.26	(−0.51, −0.01)	

LSM = least-squares mean.
Note: Studies 1, 2, 4, and 5 are randomized 28-week double-blind placebo-controlled omalizumab studies in moderate to severe asthma patients. Study 3 is a randomized 32-week double-blind placebo-controlled omalizumab study in severe asthma patients. Study 5 was not included in the analysis.
Note: The total asthma symptom score was defined as the sum of the morning asthma score, daytime asthma score, and nocturnal asthma score. The mean total asthma symptom score per day for each patient for a given period was calculated by summing the morning, daytime, and nocturnal scores in a day for that period and dividing by the number of days.
^aBased on analysis of covariance model with treatment, country, dosing schedule, and baseline mean total asthma symptom score as explanatory variables. Least-Square mean differences based on the model were calculated between treatment groups and 95% confidence intervals were constructed.
^bApplicable to study 3 only.
^cEnd of study for studies 4 and 5 was defined as the end of the 28-week double-blind period. End of study for studies 1, 2, and 3 was defined as the last observation in the double-blind stabilization phase.

TABLE 6.—Logistic regression for global evaluation of treatment effectiveness. Odds ratios and corresponding 95% confidence intervals for “good or excellent” response for omalizumab relative to placebo.

	Study 1 ^a	Study 2 ^a	Study 3 ^a	Study 4 ^b	Study 5 ^b	Pooled ^c
Investigator global evaluation						
Overall	2.24 (1.56, 3.23)	3.72 (2.59, 5.35)	2.74 (1.73, 4.34)	2.12 (1.41, 3.20)	2.15 (1.43, 3.23)	2.58 (2.16, 3.08)
≥50 yrs	3.30 (1.32, 8.28)	3.27 (1.60, 6.69)	2.69 (1.21, 5.98)	1.60 (0.79, 3.26)	1.33 (0.54, 3.27)	2.21 (1.57, 3.12)
Patient global evaluation						
Overall	2.47 (1.72, 3.55)	3.11 (2.16, 4.47)	2.61 (1.60, 4.25)	2.38 (1.58, 3.58)	1.78 (1.17, 2.71)	2.46 (2.06, 2.95)
≥50 yrs	4.56 (1.92, 10.83)	2.73 (1.35, 5.54)	3.64 (1.55, 8.58)	1.87 (0.94, 3.74)	1.00 (0.42, 2.37)	2.53 (1.79, 3.58)

^aExplanatory variables in model include treatment and sex.^bExplanatory variables in model include treatment, history of exacerbations, and sex.^cExplanatory variables in model include treatment, history of exacerbations, sex, and study.

only slightly lower than in the overall population, which was not statistically significant. The older subgroup responded to treatment with OMA in a manner consistent with the known effects of the drug dosed at levels expected to reduce serum free IgE to < 10 IU/mL (33).

Importantly, the older subgroup had more severe asthma, based on the lower percent predicted FEV₁, and the higher baseline dose of ICS. This greater severity may be explained by the longer duration of their asthma and a greater likelihood of airway remodeling. Despite this greater degree of severity, the older subgroup demonstrated a significant improvement in clinical parameters on addition of OMA to their asthma regimen. Older patients experienced a risk reduction of 28% for asthma exacerbations, experienced a clinically relevant decrease in asthma symptom scores, and were able to achieve a reduction in the use of rescue beta-2 agonists. These findings coincided with a significantly improved response to treatment as judged by patients and investigators. This is especially important in that older patients may have more fixed airway disease that is poorly responsive to treatment.

In this study, despite the higher degree of asthma severity in the older group and the incidence of co-morbidities, we found that response to treatment was similar to that in the overall patient population. We chose to perform our analy-

sis on the subgroup of patients 50 years of age and older given increasing evidence supporting a significant decline in pulmonary function among aging asthmatics (34,35), including a recent community-based study of lung function decline in older asthmatics (36). Our analysis of effect of OMA on asthma in an older subgroup supports the few observations made by others regarding treatment effects in elderly patients. Sin and Tu reported that asthma morbidity and mortality were improved in elderly asthmatics who were prescribed inhaled corticosteroids after hospitalization for asthma (7). Morbidity and mortality data indicate that the most rapid increase in asthma deaths occurred in women over age 65 and suggest that intervention strategies should concentrate on that specific population beginning in middle age (37).

Our analysis has a limitation in that it was not pre-specified. However, all outcome measures were pre-specified as part of these studies and the subgroup accounted for a substantial proportion of participating patients, thereby attenuating concerns about potential imbalances in randomization.

The safety profile of a medication established in a broader patient population may or may not be applicable to a subgroup of an older population. Pooled analysis across five clinical studies with OMA showed that the proportion of drug-related adverse events and related discontinuations were similar in

TABLE 7.—Analysis of the change from baseline in mean total rescue puffs over time in the overall population.

Period	Omalizumab		Placebo		Omalizumab vs. Placebo		
	N	LSM	N	LSM	LSM difference	95% CI	p value ^a
0–4 weeks	1089	−0.54	1054	−0.29	−0.25	(−0.44, −0.07)	
>4–8 weeks	1075	−0.72	1033	−0.20	−0.52	(−0.76, −0.29)	
>8–12 weeks	1060	−0.81	1015	−0.32	−0.50	(−0.73, −0.27)	
>12–16 weeks	1047	−1.09	996	−0.44	−0.64	(−0.89, −0.40)	
>16–20 weeks	1021	−1.11	963	−0.47	−0.64	(−0.89, −0.39)	
>20–24 weeks	1008	−1.08	953	−0.34	−0.74	(−1.00, −0.47)	
>24–28 weeks	996	−1.07	934	−0.25	−0.82	(−1.07, −0.56)	
>28–32 weeks ^b	156	−0.84	145	0.25	−1.09	(−1.71, −0.47)	
End of study ^c	1093	−0.96	1057	−0.38	−0.58	(−0.80, −0.37)	<0.0001

LSM = least-squares mean.

Note: Studies 1, 2, 4, and 5 are randomized 28-week double-blind placebo-controlled omalizumab studies in moderate to severe asthma patients. Study 3 is a randomized 32-week double-blind placebo-controlled omalizumab study in severe asthma patients.

Note: Total rescue puffs was defined as the sum of AM and PM puffs. The mean total rescue puffs per day for each patient for a given period was calculated by summing the number of puffs taken in a day for that period and dividing by the number of days.

^aBased on analysis of covariance model with treatment, country, dosing schedule, and baseline mean total rescue puffs as explanatory variables. Least-Square mean differences based on the model were calculated between treatment groups and 95% confidence intervals were constructed.

^bApplicable to study 3 only.

^cEnd of study for studies 4 and 5 was defined as the end of the 28-week double-blind period. End of study for studies 1, 2, and 3 was defined as the last observation in the double-blind stabilization phase.

TABLE 8.—Analysis of the change from baseline in mean total rescue puffs over time in the ≥50 years of age subgroup.

Period	Omalizumab		Placebo		Omalizumab vs. Placebo		
	N	LSM	N	LSM	LSM difference	95% CI	p value ^a
0–4 weeks	284	–0.50	292	–0.31	–0.19	(–0.55, 0.16)	0.0414
>4–8 weeks	281	–0.68	283	–0.30	–0.37	(–0.81, 0.06)	
>8–12 weeks	280	–0.58	281	–0.37	–0.21	(–0.66, 0.24)	
>12–16 weeks	278	–0.80	275	–0.53	–0.27	(–0.75, 0.21)	
>16–20 weeks	274	–0.81	266	–0.32	–0.49	(–1.01, 0.02)	
>20–24 weeks	268	–0.52	262	–0.12	–0.40	(–0.94, 0.14)	
>24–28 weeks	268	–0.48	258	–0.04	–0.44	(–0.95, 0.07)	
>28–32 weeks ^b	58	–0.97	48	0.12	–1.09	(–2.35, 0.17)	
End of study ^c	285	–0.78	293	–0.31	–0.47	(–0.92, –0.02)	

LSM = least-squares mean.
Note: Studies 1, 2, 4, and 5 are randomized 28-week double-blind placebo-controlled omalizumab studies in moderate to severe asthma patients. Study 3 is a randomized 32-week double-blind placebo-controlled omalizumab study in severe asthma patients.
Note: Total rescue puffs was defined as the sum of AM and PM puffs. The mean total rescue puffs per day for each patient for a given period was calculated by summing the number of puffs taken in a day for that period and dividing by the number of days.
^aBased on analysis of covariance model with treatment, country, dosing schedule, and baseline mean total rescue puffs as explanatory variables. Least-Square mean differences based on the model were calculated between treatment groups and 95% confidence intervals were constructed.
^bApplicable to study 3 only.
^cEnd of study for studies 4 and 5 was defined as the end of the 28-week double-blind period. End of study for studies 1, 2, and 3 was defined as the last observation in the double-blind stabilization phase.

the older subgroup compared to the overall population. This provides information as to the safety and tolerability of OMA in older patients.

Practicing physicians should be more aware of the prevalence and severity of asthmatic disease in the older patient where it remains an important public health issue that is underappreciated, often misdiagnosed, under-treated, and characterized by significant morbidity and mortality. With improved recognition of disease in this older population, improved management may follow. The use of OMA in older patients with IgE-mediated asthma provides an effective addition to treatment when symptoms persist despite recommended doses of ICS.

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