

ORIGINAL ARTICLE

Effect of omalizumab on the need for rescue systemic corticosteroid treatment in patients with moderate-to-severe persistent IgE-mediated allergic asthma: a pooled analysis

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ABSTRACT

Background: Allergic asthma is an immunoglobulin E (IgE)-mediated disease characterized by frequent exacerbations following exposure to relevant allergens that leads to the development of chronic airway inflammation. Omalizumab, an anti-IgE antibody, reduces asthma exacerbation and hospitalization rates in patients with IgE-mediated allergic asthma. We investigated the effect of omalizumab on asthma outcomes in a retrospective pooled analysis of data from phase III clinical trials in patients (≥ 12 years) with moderate-to-severe persistent IgE-mediated allergic asthma.

Methods: Systemic corticosteroid bursts and physician and patient overall assessments of asthma control were assessed in patients who received add-on omalizumab or current asthma therapy (control). The association of physician and patient overall assessments with the number of steroid bursts were also evaluated.

Results: The analysis encompassed 4308 patients with moderate-to-severe persistent IgE-mediated allergic asthma (93% met GINA

2002 criteria for severe persistent asthma) from seven clinical trials. The number of systemic corticosteroid bursts was significantly lower in omalizumab-treated patients than in the control group (relative risk [95% CI]: 0.57 [0.48–0.66], $p < 0.001$). In addition, 58.5% of omalizumab recipients had complete/marked improvement in asthma control according to the physician's overall assessment (responders) vs. 36.9% in the control group ($p < 0.001$). Similarly, 64.2% of omalizumab patients vs. 43.9% of control patients had complete/marked improvement according to the patient's overall assessment ($p < 0.001$). There were statistically significant associations between systemic corticosteroid bursts and physician (Goodman–Kruskal gamma [95% CI]: 0.32 [0.26–0.38]) and patient (gamma [95% CI]: 0.29 [0.23–0.36]) overall assessments. This pooled analysis has limitations as it was not pre-specified.

Conclusions: Omalizumab therapy reduced the need for systemic corticosteroid bursts and improved effectiveness of asthma treatment as judged by both physicians and patients.

Introduction

Current asthma management guidelines (e.g., National Heart, Lung, and Blood Institute [NHLBI], National Asthma Education and Prevention Program [NAEPP]¹, and Global Initiative for Asthma [GINA]² guidelines) classify asthma as intermittent, mild persistent, moderate persistent or severe persistent and recommend a stepwise approach to asthma treatment. Asthma control is defined similarly in the NAEPP and GINA guidelines and includes aspects of symptom control, pulmonary function, activity levels, prevention of asthma exacerbations and asthma-related mortality^{1,2}. For treatment of mild intermittent asthma, the use of rescue bronchodilators as needed is recommended, with increasing doses of inhaled corticosteroids (ICS) used to control mild, moderate and severe persistent asthma. In addition, for patients with moderate or severe persistent asthma, long-acting β_2 -agonists (LABAs) may also be added. However, a substantial proportion of patients with persistent asthma are inadequately controlled despite high doses of ICS and a LABA as recommended in international guidelines for the treatment of moderate-to-severe asthma¹⁻⁴. For patients who do not respond to ICS or various additional classes of treatment, such as short-acting β_2 -agonist bronchodilators, LABAs and leukotriene modifiers, the clinician will often need to resort to systemic corticosteroids typically administered in short bursts over 5–7 days, either via oral or parenteral routes, to re-establish asthma control. Therefore, the need for steroid bursts is an important marker of the instability of asthma and can be used to judge asthma control.

The short-term use of systemic corticosteroids was previously thought to be relatively innocuous; however, more recent data suggests that combining frequent periodic bursts in patients already taking high doses of ICS can increase mood disturbances⁵, the risk of atrial fibrillations⁶, and the risk of osteoporosis⁷. These effects can be compounded, over the long term, by other side-effects including weight gain, glaucoma, cataracts, cardiovascular disease, skeletal effects such as growth retardation in the young and increasing risk for osteoporosis and its sequelae in middle age and older patients^{1,8,9}.

It is estimated that two-thirds of asthma has an allergic component¹⁰. The cross-linking by allergen of immunoglobulin E (IgE) bound to high-affinity IgE receptors (Fc ϵ RI) on mast cells and basophils initiates the inflammatory cascade through release of a variety of mediators, including histamine, leukotrienes (LT), and platelet-activating factor^{10,11}. Omalizumab is a humanized monoclonal anti-IgE antibody, which reduces serum free IgE via specific binding to a domain common to IgE of all specificities. Binding leads to sequestration and removal of IgE from the circulation^{12,13}. Omalizumab has been shown to reduce

exacerbation rates and improve quality of life (QoL) in patients with moderate-to-severe and severe persistent IgE-mediated allergic asthma¹⁴⁻²⁵.

To further evaluate the efficacy of omalizumab in patients with poorly controlled IgE-mediated allergic asthma despite use of multiple asthma controller medications, we studied the effects of omalizumab treatment on asthma control as measured by rescue use of systemic corticosteroid bursts. In addition, we assessed treatment effectiveness by analysis of physician's and patient's ratings of asthma therapy.

Methods

This pooled analysis identified phase III clinical trials that assessed the efficacy of omalizumab in patients with moderate-to-severe persistent IgE-mediated allergic asthma. Randomized, double-blind, placebo-controlled trials and randomized open-label trials were included. Only patients ≥ 12 years of age were included in the analysis.

Efficacy outcomes

Rescue use of systemic corticosteroid bursts (oral or intravenous) and the effectiveness of therapy was evaluated using the physician (investigator) or patient overall assessment of treatment effectiveness based on a five-level evaluation that categorized control as complete (= 1), markedly improved (= 2), discernible but limited improvement (= 3), no appreciable change (= 4), or worsened (= 5). For the purposes of this pooled analysis, response on these outcomes was further categorized. Responders to treatment were unequivocal and defined as those with complete control or marked improvement in control; those that were judged not to have responded comprised the remainder (non-responders). We also assessed the association of the physician and patient overall rating of control to the number of systemic corticosteroid bursts. The effect of omalizumab on corticosteroid bursts was also assessed according to the physician's overall assessment classification; QoL (Asthma Quality of Life Questionnaire [AQLQ] score²⁶) and forced expiratory volume in 1 second (FEV₁) were also assessed to provide additional outcomes data for omalizumab according to the physician's overall assessment classification.

Statistical analysis

The number of systemic corticosteroid bursts was analyzed using a Poisson regression model with treatment, age, sex, use of systemic corticosteroids at baseline, baseline FEV₁ and study as (pre-specified)

explanatory variables^{27,28}. Poisson regression analysis provides a relative risk of systemic corticosteroid bursts. The relative risk of systemic corticosteroid bursts for omalizumab versus control was calculated by exponentiating the treatment parameter estimate and presented with corresponding 95% confidence interval (CI).

The dichotomized (responder/non-responder) physician and patient overall assessments were analyzed using the Cochran–Mantel–Haenszel test²⁸. The association between the number of systemic corticosteroid bursts and the physician or patient overall assessments was determined by calculating Goodman–Kruskal gamma and 95% CIs²⁸. Changes from baseline in the overall AQLQ score and FEV₁ were analyzed using analysis of covariance (ANCOVA). The ANCOVA model for the change from baseline in the overall AQLQ score included treatment, age, sex, baseline score, and study as (pre-specified) explanatory variables. Similarly, the ANCOVA model for the change from baseline in FEV₁ included treatment, age, sex, baseline FEV₁, and study as explanatory variables. Least squares mean (LSM) differences (omalizumab–placebo) [95% CI] from ANCOVA are presented. All statistical analyses were performed using SAS software, Version 8.2.

Results

Studies included in the pooled analysis

This pooled analysis identified seven randomized, controlled trials that assessed efficacy and safety

of omalizumab in the treatment of patients with moderate-to-severe persistent IgE-mediated allergic asthma (93% of patients met GINA 2002 criteria for severe persistent asthma based on both clinical features and asthma therapy) (Table 1). In total, five of the trials were randomized, double-blind, placebo-controlled studies^{14,16–21} and two were randomized, controlled open-label studies^{15,22}. In all studies, omalizumab was given as add-on therapy to current asthma treatment and compared with current asthma therapy alone ($\pm$ placebo). Omalizumab was administered subcutaneously every 2 or 4 weeks according to patients' bodyweight and baseline IgE levels. Further details of the seven study designs and individual study results are described elsewhere^{14–23}.

Rescue use of systemic corticosteroid bursts (oral or intravenous) was recorded in all seven trials and the physician's/patient's overall assessment was recorded in the five placebo-controlled trials.

Patient characteristics

The baseline demographic and clinical characteristics of the pooled patient population were similar and are presented in Table 2. There were 2511 patients in the omalizumab-treated group and 1797 patients in the control group. At study entry, patients were taking high doses of ICS (mean dose beclometasone dipropionate [BDP] equivalent 1462 μ g/day; omalizumab 1464 μ g/day; control 1459 μ g/day, $p = 0.862$). In addition to ICS, 57.3% of patients also received LABAs (omalizumab

Table 1. Studies included in the pooled analysis

Study	Patient population	Patients with severe persistent asthma* n (%)	Study treatment arms†	Duration
Study 1 ¹⁴	Inadequately controlled severe asthma despite GINA 2002 step 4 therapy	419 (100)	Omalizumab + CAT vs. placebo + CAT	28 weeks
Study 2 ¹⁵	Inadequately controlled moderate-to-severe asthma	294 (94.2)	Omalizumab + CAT vs. CAT alone	52 weeks
Study 3 ¹⁶	Moderate-to-severe asthma and rhinitis	364 (89.9)	Omalizumab + CAT vs. placebo + CAT	28 weeks
Study 4 ^{17,18}	Severe asthma	523 (99.6)	Omalizumab + CAT vs. placebo + CAT	52 weeks (28 weeks + 24-week extension)
Study 5 ^{19,20}	Moderate-to-severe asthma	537 (98.4)	Omalizumab + CAT vs. placebo + CAT	52 weeks (28 weeks + 24-week extension)
Study 6 ²¹	Severe asthma dependent on high-dose ICS	315 (92.4)	Omalizumab + CAT vs. placebo + CAT	32 weeks
Study 7 ²²	Moderate-to-severe asthma	1556 (88.4)	Omalizumab + CAT vs. CAT alone	24 weeks

*Severe persistent asthma according to GINA 2002 classification based on both clinical features and asthma therapy
†All patients were receiving ICS; LABAs were not used in studies 4 and 5
CAT = current asthma therapy; GINA = Global Initiative for Asthma; ICS = inhaled corticosteroids; LABA = long-acting β_2 -agonists

Table 2. Baseline demographic and clinical characteristics

	Omalizumab (n = 2511)	Control (n = 1797)	p-value
Age, years			0.086†
Mean (SD)	41.6 (14.83)	40.9 (14.43)	
Range	12–79	12–76	
Sex, n (%)			0.729‡
Males	1018 (40.5)	738 (41.1)	
Females	1493 (59.5)	1059 (58.9)	
Race, n (%)			0.758‡
Caucasian	2137 (85.1)	1526 (84.9)	
Black	173 (6.9)	114 (6.3)	
Oriental	36 (1.4)	27 (1.5)	
Other	165 (6.6)	130 (7.2)	
Serum total IgE (IU/mL), mean (SD)	198.2 (161.43)	200.2 (160.15)	0.690†
Baseline ICS in BDP equivalent (µg/day), mean (SD)	1464.4 (1050.97)	1458.9 (1004.06)	0.862†
Baseline oral corticosteroid use, n (%)			0.186‡
Yes	273 (10.9)	173 (9.6)	
No	2238 (89.1)	1624 (90.4)	
Baseline LABA use, n (%)			< 0.001‡
Yes	1537 (61.2)	933 (51.9)	
No	974 (38.8)	864 (48.1)	
FEV ₁ , % of predicted, mean (SD)	70.3 (17.65)	70.0 (17.34)	0.576†
Reversibility (%), mean (SD)	24.0 (19.29)	23.6 (18.93)	0.529†
Baseline total clinical symptom score*, mean (SD)	7.7 (8.29)	6.8 (7.41)	0.005†
Number of doctor's office visits in the past year*, mean (SD)	2.9 (4.54)	2.6 (4.24)	0.047†
Missed school or work days due to asthma in the past year*, mean (SD)	13.1 (36.93)	12.9 (38.76)	0.909†
Number of emergency room visits in the past year, mean (SD)	0.7 (1.79)	0.7 (1.91)	0.615†
Hospitalization in the past year*, n (%)	359 (14.3)	251 (14.0)	0.876‡
Ever intubated, n (%)	135 (5.4)	76 (4.2)	0.065‡

*Not collected for study 722

†two-sided *t*-test for comparing treatment groups, assuming unequal variances between treatment groups

‡Pearson χ^2 test for comparing treatment groups

BDP = beclometasone dipropionate; FEV₁ = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; IgE = immunoglobulin E; LABA = long-acting β_2 -agonist; SD = standard deviation

61%; control 52%, $p < 0.001$). Chronic oral daily corticosteroids were used at baseline in 10.4% of patients (omalizumab 10.9%; control 9.6%, $p = 0.186$). In accordance with study entry criteria, patients remained symptomatic despite use of multiple controller medications.

Need for systemic corticosteroid bursts and asthma control

The number of systemic steroid bursts was significantly reduced in omalizumab-treated patients compared with the control group [relative risk [95% CI]: 0.57

[0.48–0.66], $p < 0.001$). It would be expected that a patient treated with add-on omalizumab would require 43% fewer systemic steroid bursts than would be required had the patient remained on current asthma therapy alone ($\pm$ placebo). The mean ($\pm$ standard deviation) number of systemic corticosteroid bursts was 0.4 ± 0.87 in the omalizumab-treated group and 0.6 ± 1.24 in the control group.

In the five placebo-controlled trials, patients receiving omalizumab were also more likely to be categorized as responders (complete control or marked improvement in control) than patients in the control group for both the physician and patient overall assessments (Figure 1).

For the physician evaluation, 58.5% of omalizumab recipients ($n = 665$) were defined as responders, compared with 36.9% of patients in the control group ($n = 406$). Similarly, as judged by patients, 64.2% ($n = 729$) of omalizumab patients vs. 43.9% ($n = 483$) of control patients were categorized as responders.

Paralleling these findings, an analysis of the physician and patient overall assessments by number of systemic corticosteroid bursts showed that patients with smaller numbers of systemic corticosteroid bursts were more likely to have experienced complete control or marked improvement in control than patients with larger numbers of systemic corticosteroid bursts (Figure 2). Moreover, there were statistically significant associations between systemic corticosteroid bursts and both the physician (Goodman–Kruskal gamma [95% CI]: 0.32 [0.26–0.38], $p < 0.001$) and patient (gamma [95% CI]: 0.29 [0.23–0.36], $p < 0.001$) overall assessments.

The reduction in corticosteroid bursts with omalizumab in the five placebo-controlled trials (relative risk [95% CI]: 0.65 [0.55–0.77], $p < 0.001$) (Table 3) was similar to that seen in the overall pooled analysis.

In addition, omalizumab was associated with significant decreases in corticosteroid bursts in responders judged by physician's overall assessment (complete/marked improvement in control), but not for patients judged to have experienced limited improvement or no appreciable change/worsening control (Table 3). Similarly, omalizumab significantly improved QoL (change from baseline in overall AQLQ score) in patients receiving omalizumab compared with placebo recipients in the overall population in the five placebo-controlled trials (0.96 vs. 0.62; LSM difference [95% CI]: 0.33 [0.25–0.42], $p < 0.001$) (Table 3). Responders to omalizumab experienced a significantly greater improvement in QoL than the placebo group, whereas QoL was not significantly different from placebo in patients with a limited improvement or no appreciable change/worsening in control (Table 3). Although relatively modest, a significantly greater improvement in FEV₁ (change from baseline) was seen in patients receiving omalizumab compared with those receiving placebo in the overall population in the five placebo-controlled trials (LSM difference [95% CI] mL: 75.27 [44.56–105.98],

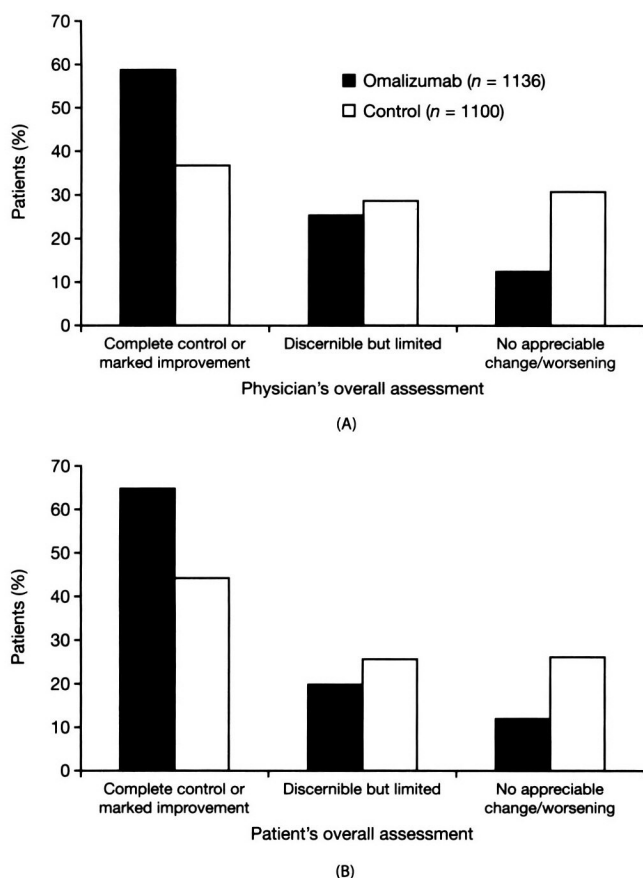


Figure 1. Physician's (panel A) and patient's (panel B) overall assessments of asthma control in patients receiving omalizumab or control therapy. Data were missing for 101 patients for the physician's overall assessment and for 109 patients for the patient's overall assessment; $p < 0.001$ for omalizumab versus control

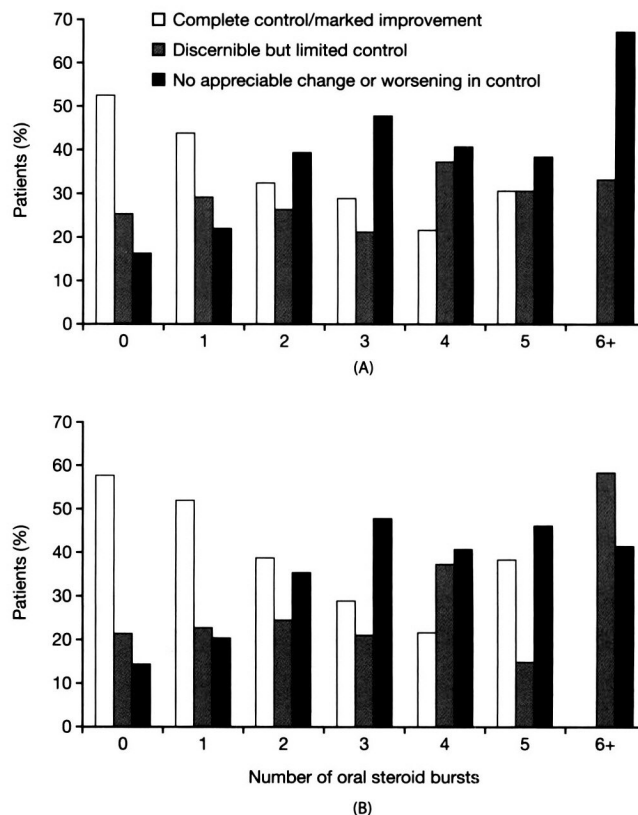


Figure 2. Physician's (panel A) and patient's (panel B) overall assessments of asthma control by number of systemic corticosteroid bursts in the total pooled analysis population. Data were missing for 100 patients for the physician's overall assessment and for 110 patients for the patient's overall assessment; $p < 0.001$ for the association (Goodman–Kruskal gamma) between number of steroid bursts and physician's and patient's overall assessments

Table 3. Relative risk of steroid bursts, change from baseline in QoL and FEV₁ in patients classified according to physician's overall assessment

Outcome	Physician's overall assessment			
	Overall	Complete control/marked improvement	Limited improvement in control	No appreciable change or worsening asthma control
Relative risk (omalizumab: placebo) of steroid bursts, [95% CI]	0.65 [0.55, 0.77] <i>p</i> < 0.001	0.69 [0.53, 0.89] <i>p</i> = 0.004	0.87 [0.63, 1.20] <i>p</i> = 0.395	0.94 [0.71, 1.25] <i>p</i> = 0.678
Change from baseline in overall AQLQ score, LSM difference (omalizumab-placebo) [95% CI]	0.33 [0.25, 0.42] <i>p</i> < 0.001	0.35 [0.24, 0.46] <i>p</i> < 0.001	0.02 [-0.12, 0.17] <i>p</i> = 0.759	-0.09 [-0.29, 0.11] <i>p</i> = 0.373
Change from baseline in FEV ₁ (mL), LSM difference (omalizumab-placebo) [95% CI]	75.27 [44.56, 105.98] <i>p</i> < 0.001	71.90 [27.21, 116.60] <i>p</i> = 0.001	-1.14 [-62.11, 59.82] <i>p</i> = 0.970	30.00 [-41.50, 101.51] <i>p</i> = 0.410

AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; FEV₁ = forced expiratory volume in 1 second; LSM = least squares mean

p < 0.001) (Table 3). In responders, change from baseline in FEV₁ was significantly greater in the omalizumab group than in the placebo group, whereas FEV₁ was not significantly different from placebo in patients with a limited improvement or no appreciable change/worsening in control (Table 3).

Discussion

NHLBI and GINA guidelines define a number of goals for asthma management, including achieving and maintaining control of symptoms, maintaining pulmonary function as close to normal levels as possible, improving activities of daily living while avoiding adverse effects from asthma medications^{1,2}. ICS are fundamental to the treatment of asthma and have an acceptable side-effect profile. However, the use of systemic corticosteroids can be a major cause of morbidity, especially in children and older adults, causing multiple metabolic and immune adverse effects with acute and chronic administration that can have both short-term and longer-term consequences^{2,5-9}.

The results of this pooled analysis provide evidence of the value of add-on therapy with omalizumab to achieve the goals of asthma management set out in the NHLBI and GINA guidelines^{1,2}. Across the seven clinical trials, there was a 43% reduction in the risk of requiring systemic corticosteroid bursts in patients receiving omalizumab compared with control treatment. This finding is consistent with an earlier report of a 38% reduction in exacerbation rates observed in patients randomized to omalizumab in a pooled analysis of omalizumab trials²³. This present analysis was performed to look specifically at the effect of omalizumab on the need for steroid bursts, patient/physician overall assess-

ment of treatment effectiveness and the correlation between the two, and adds to previously published pooled data²³. Data on corticosteroid bursts are of particular relevance given recent evidence suggesting that the significant side-effects of corticosteroids are not limited to long-term use⁵⁻⁹.

The reduction in corticosteroid bursts with omalizumab paralleled improvements in physician and patient overall assessment of treatment effectiveness, showing that improvements in clinical status were achieved while also reducing systemic corticosteroids, supporting the notion that these reductions were the direct result of improvements in asthma control. Omalizumab may thereby help patients avoid potential adverse effects of systemic corticosteroids while improving overall asthma control.

This pooled analysis also demonstrated similar results for physician overall assessment and the patient overall assessment. In addition, patient overall assessment correlated with reductions in corticosteroid burst requirements. This observation indicates the potential usefulness of patient assessment of asthma status on a population level and supports the use of this type of evaluation to provide a comprehensive and meaningful assessment of overall asthma control in a clinic setting. The present study also showed a significant reduction in the relative risk of steroid bursts and significant improvements in both QoL and lung function only in patients who were judged by physicians to have responded to therapy with omalizumab. There were no significant differences in relative risk of steroid bursts in patients classified as achieving limited but discernible control or poor/worsening control between the two treatment groups.

This pooled analysis has limitations as it was not pre-specified. However, the outcome measures used

were pre-specified as either primary or secondary for each of the trials that were included in the pooled analysis. Another limitation of the pooled analysis was that it combined data from randomized, double-blind, placebo-controlled trials with data from randomized, controlled, open-label trials. However, patient populations and methodologies were similar, for example, all patients had IgE-mediated allergic asthma, 90–100% of patients met GINA 2002 criteria for severe persistent asthma across studies and omalizumab was added to current asthma therapy every 2 or 4 weeks in all studies. Pooled baseline demographic and clinical characteristics were generally similar between the two treatment groups, although there were some significant differences in some baseline measures, most notably, in LABA use. However, we found no evidence of statistical interaction or substantive changes in results if this term was used as a covariate. In addition, the relative risk (omalizumab : control) of a steroid burst using data from all seven trials (0.57) was similar to that obtained for the five placebo-controlled trials (0.65). Therefore, an important strength of this analysis is that it provides a summary of the total available data for omalizumab, which does not appear to have been substantively affected by combining data from placebo-controlled and open-label studies.

Conclusion

This pooled analysis of seven clinical trials to examine the efficacy of omalizumab in the treatment of moderate-to-severe persistent IgE-mediated allergic asthma, suggests that adding omalizumab to current asthma therapy significantly improves disease control both in terms of reducing the need for systemic corticosteroid bursts as well as in improving assessments of control judged by physicians and the patients themselves.

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