

Effect of omalizumab on lung function and eosinophil levels in adolescents with moderate-to-severe allergic asthma



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ABSTRACT

Background: Omalizumab improves clinical outcomes in patients with asthma. Several studies have shown lung function improvements with omalizumab; however, this has not been examined exclusively in adolescents.

Objective: To assess the effect of omalizumab on lung function and eosinophil counts in adolescents with uncontrolled moderate-to-severe allergic asthma.

Methods: In this post hoc analysis, data from adolescents aged 12 to 17 years from 8 randomized trials of omalizumab were pooled (studies 008, 009, and 011, and SOLAR, INNOVATE, ALTO, ETOPA, and EXTRA). Changes from baseline to end of study in forced expiratory volume in 1 second (FEV₁), percent predicted FEV₁ (ppFEV₁), forced vital capacity (FVC), and blood eosinophil counts were assessed by fitting an analysis of covariance model and calculating least squares mean (LSM) difference for omalizumab vs placebo.

Results: A total of 340 adolescents were identified (omalizumab, n = 203 [59.7%]; placebo, n = 137 [40.3%]). Omalizumab increased all baseline lung function variables more than placebo by end of study: LSM treatment differences (95% confidence interval) were 3.0% (0.2%–5.7%; P = .035), 120.9 mL (30.6–211.2 mL; P = .009), and 101.5 mL (8.3–194.6 mL; P = .033) for ppFEV₁, absolute FEV₁, and FVC, respectively. The LSM difference demonstrated a greater reduction in eosinophil counts for omalizumab vs placebo: –85.9 cells/μL (–137.1 to –34.6 cells/μL; P = .001).

Conclusion: Omalizumab was associated with lung function improvements and circulating eosinophil counts reductions in adolescents with moderate-to-severe uncontrolled asthma. Findings emphasize the effect of omalizumab in young patients and the need to optimize treatment early in the disease course. [: NCT00314574, NCT00046748, NCT00401596](https://clinicaltrials.gov/)

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Introduction

Asthma is one of the most common chronic diseases in young people, with an estimated prevalence of 8.3%.¹ Although guidelines exist for the treatment of asthma,² studies suggest that approximately 50% of patients remain inadequately controlled.³ Factors contributing to lack of asthma control include improper use of inhalers, a failure to control environmental exposure to triggers, and the presence of untreated comorbidities.^{4–7} Poor adherence to medication has been described in up to 45% of patients and also has been associated with poor asthma control.³ Furthermore, lack of provision of medications from primary care physicians is a contributing factor.⁸

Failure to adequately control asthma during childhood or adolescence may negatively affect clinical outcomes, quality of life, and health care resource utilization.⁹ Indeed, uncontrolled asthma is associated with reduced lung function growth during childhood,¹⁰ lower maximally attained lung function, and accelerated lung function decline in adulthood.¹¹ A post hoc analysis of 2 large studies of severe asthma demonstrated that patients who had experienced 3 or more exacerbations demonstrated losses of postbronchodilator forced expiratory volume in 1 second (FEV₁) of up to 77 mL/year,¹² which is considerably higher than the approximate 20-mL/year loss observed in healthy adults.^{11,12} The loss of such substantial lung function may lead to life-threatening lung function impairment.¹¹ Adolescence reflects a crucial time to intervene in asthma treatment because lung function gains peak in puberty,¹³ and adolescents experience larger improvements in lung function than adults after asthma treatment.¹⁴ These changes in lung function have significant long-term impacts, with patients maintaining gains in lung function into early adulthood.¹⁵

Immunoglobulin E (IgE) is a central player in allergic asthma¹⁶ and is frequently elevated in asthmatics with severe disease¹⁷ and those with a history of atopy.¹⁸ Omalizumab, a humanized monoclonal antibody against IgE, was approved for treatment of asthma in 2003¹⁹ and has been shown to improve asthma symptoms, reduce the frequency of exacerbations,^{20–22} and reduce health care utilization and school absenteeism.²³ Additionally, some studies have indicated that omalizumab improves lung function.^{20,22} Although significant improvements in lung function have been shown in adolescents in real-world studies,²⁴ the effect of omalizumab on lung function of adolescent patients in placebo-controlled trials has not been established.

This post hoc analysis examined pooled spirometry measurements from 8 clinical trials of adolescents receiving either omalizumab or placebo to assess the effect of omalizumab therapy on lung function in adolescents with uncontrolled moderate-to-severe allergic asthma.

Methods

Data from adolescent patients from 8 randomized, placebo-controlled, multicenter omalizumab studies were pooled for this analysis. All participants provided written informed consent, and the study protocols were approved by relevant ethics committees or institutional review boards.^{20–22,25–29} Patients aged 12 to 75 years, or 6 to 75 years in ALTO, were randomized to receive omalizumab or placebo every 2 or 4 weeks for a treatment period between 24 and 52 weeks.^{20–22,25–29} Omalizumab dosing and dosing intervals were based on weight and baseline IgE levels of the patients as described in the prescribing information.¹⁹ Detailed methods have been published previously, with the exception of ALTO.^{20–22,25–29} Study design and entry criteria for each study are briefly summarized below and in Table 1.

Study 008

Study 008²⁰ was a double-blind parallel-group trial in patients with allergic asthma of at least 1-year duration whose condition remained uncontrolled despite inhaled corticosteroids (ICS). Patients were required to have percent predicted FEV₁ (ppFEV₁) 40% to 80%, an increase in FEV₁ of at least 12% within 30 minutes after albuterol, and a total IgE level between 30 and 700 IU/mL at screening. All patients were switched to beclomethasone dipropionate (BDP), the dose of which was altered to maintain asthma control. Stable BDP dose was maintained for 4 weeks before randomization and during the 4-month steroid-stable period. Beclomethasone dipropionate was tapered by 25% of the baseline dose every 2 weeks for 8 weeks until discontinuation or worsening of asthma symptoms. Rescue salbutamol was permitted throughout the study. Spirometry was performed every 2 or 4 weeks before dosing and 1 hour after each dose.²⁰

Study 009

Study 009²⁵ was a double-blind parallel-group study in patients with stable allergic asthma for at least 1-year duration who had no changes in asthma medication or acute exacerbations requiring corticosteroids for at least 1 month before screening. Patients were required to have an IgE level between 30 and 700 IU/mL, body weight up to 150 kg, ppFEV₁ between 40% and 80%, and an increase in ppFEV₁ of at least 12% within 30 minutes of salbutamol administration, and they had to be receiving treatment with the equivalent of BDP 500 to 1200 µg/day for at least 3 months at screening. During the 4- to 6-week run-in period, patients were switched from their current corticosteroid medication to equivalent doses of BDP. The BDP dose was maintained during the 16-week steroid-stable phase and then reduced by 25% every 2 weeks during the 12-week steroid-reduction phase until discontinuation or at least 20% reduction in FEV₁ was observed. Rescue salbutamol was permitted throughout the study. Spirometry was performed at weeks 0 (baseline), 4, 8, 12, 16, 18, 20, 22, 24, 26, and 28.²⁵

Study 011

Study 011²² was a double-blind trial in patients with severe asthma requiring fluticasone propionate 1000 µg/day or more for symptom control, and a total IgE level of 30 to 700 IU/mL. Patients were switched to fluticasone propionate, with the dose optimized during the 6- to 10-week run-in period and maintained for at least 4 weeks before the 32-week double-blind treatment period. During the final 16 weeks of the double-blind treatment period, the fluticasone propionate dose was gradually tapered by 250 µg/day at 2-week intervals until discontinuation or symptom recurrence. Short-acting β₂-agonists were permitted, as required, as was continued use of long-acting β₂-agonists (LABAs). Lung function was measured at weeks 4, 20, 28, and 30.²²

SOLAR

The Study of Omalizumab in comorbid Asthma and Rhinitis (SOLAR)²⁶ was a double-blind trial in patients with moderate-to-severe allergic asthma for at least 1 year and concomitant persistent allergic rhinitis for at least 2 years. Patients were required to have been receiving ICS 400 µg/day or more and to have had at least 2 unscheduled visits related to asthma in the past year, a ppFEV₁ increase of at least 12% after salbutamol administration, and a total IgE level of 30 to 1300 IU/mL at screening to be eligible for study entry. All patients were switched to BDP, the dose of which remained constant during the 4-week run-in period. During the 28-week double-blind period, ICS dose was altered at the study physician's discretion. Lung function was measured at baseline and end of study.²⁶

INNOVATE

INNOVATE²⁷ was a double-blind parallel-group study in patients with severe persistent allergic asthma inadequately controlled despite high-dose ICS and LABAs.²⁷ Patients were required to have ppFEV₁ between 40% and 80%, FEV₁ reversibility at least 12% from baseline within 30 minutes of inhaled salbutamol, and a total IgE level of 30 to 700 IU/mL at screening. During the first 4 weeks of the 8-week run-in phase, asthma medications were adjusted to achieve optimal control. Eligible patients then entered a 28-week treatment phase. Concomitant controller medication doses remained constant throughout the study. Short-acting β_2 -agonists were permitted as rescue medications. Spirometry was performed every 2 weeks during run-in; at weeks 0, 2, 4, 12, 20, and 28 of the treatment phase; and at weeks 4 and 16 of follow-up.²⁷

ALTO

ALTO²⁹ was an open-label controlled safety trial in patients with moderate-to-severe persistent asthma. Patients were required to have ppFEV₁ below 80% or a history of ppFEV₁ below 80%, IgE levels between 30 and 1300 IU/mL, and body weight between 20 and 150 kg at screening. Patients were required to be on moderate, but stable, daily doses of any ICS or oral corticosteroid for at least 30 days before screening, and an additional controller. After the 2-week screening period, patients were randomized to either omalizumab or placebo for 24 weeks. Lung function was measured at baseline and week 24.²⁹

ETOPA

ETOPA²⁸ was an open-label parallel-group study in patients with persistent, uncontrolled, moderate-to-severe allergic asthma. Patients were required to have FEV₁ reversibility of 12% within 30 minutes of receiving salbutamol 400 μ g, IgE levels of 30 to 700 IU/mL, and to be receiving BDP 400 μ g/day or more at baseline. Patients received best standard care consisting of ICS/oral corticosteroids and LABA as required, with omalizumab or placebo for 12 months. Rescue medication with salbutamol was permitted throughout the study. Spirometry was performed at months 3, 6, 9, and 12 of treatment and after a 4-week follow-up phase.²⁸

EXTRA

EXTRA²¹ was a 48-week, prospective, double-blind, parallel-group study in patients with severe asthma that remained uncontrolled despite high-dose ICS and LABAs. Patients were also required to have prebronchodilator ppFEV₁ of 40% to 80%, serum IgE levels of 30 to 700 IU/mL, and body weight between 30 and 150 kg. Omalizumab or matching placebo were added to the patient's current medications. No adjustment of any medication was permitted during the study. Systemic steroids and albuterol were permitted for management of an asthma exacerbation and as a rescue medication throughout the study. Spirometry was performed every 4 weeks from weeks 0 to 48.²¹

Assessments

Patient demographics, lung function data (ppFEV₁, FEV₁, forced vital capacity [FVC]), and history of exacerbations were collected from adolescent patients (aged 12–17 years) in studies 008, 009, and 011, and EXTRA, INNOVATE, ALTO, ETOPA, and SOLAR, and pooled for this post hoc analysis. Lung function was evaluated using spirometry at baseline and end of study, defined as the assessment closest to week 28 post treatment. For the 3 studies that included a steroid-reduction phase (008, 009, 011), end of study was the last nonmissing observation in the double-blind steroid-stable phase at week 16. The end-of-study spirometry measurement was obtained

at week 28 for SOLAR, INNOVATE, and EXTRA; week 24 for ALTO; and week 27 for ETOPA. Forced vital capacity data were not collected from ETOPA.

Blood eosinophil counts were measured at baseline and the assessment closest to the week 28 visit. The end-of-study eosinophil count measurement was obtained at week 16 (end of double-blind stable-dose phase) for studies 008, 009, and 011; week 28 for SOLAR and INNOVATE; week 32 for EXTRA; and week 53 for ETOPA. Eosinophil counts were not collected in ALTO. Safety analyses from these studies have been reported previously.^{20–22,25–28}

Statistical Analysis

Patient demographics and clinical characteristics were collected at baseline and summarized using descriptive statistics. The least squares mean (LSM) change from baseline in FEV₁, FVC, and eosinophil counts in both groups; LSM treatment difference and its 95% confidence interval (CI); and *P* values were based on an analysis of covariance (ANCOVA) model that included treatment, baseline value, and study as explanatory variables. The LSM for each treatment group is adjusted for the effect of explanatory variables and is obtained from fitting an ANCOVA model to the data. Accordingly, LSM treatment difference is adjusted for any potential imbalances in the distribution of explanatory variables included in the ANCOVA model.³⁰

Results

Patient Demographics and Clinical Characteristics

Of 340 adolescents identified across 8 studies, 203 (59.7%) received omalizumab and 137 (40.3%) received placebo (Table 1). Baseline demographic and clinical characteristics were generally similar between omalizumab- and placebo-treated groups (Table 2). Most patients were male (63% in both groups) and white (76.8% vs 70.8% for omalizumab- and placebo-treated groups, respectively), and a similar mean (standard deviation [SD]) age was noted in both omalizumab- and placebo-treated groups (14.1 [1.7] years).

Lung Function

At the study assessment closest to week 28, patients receiving omalizumab experienced greater improvements in all lung function variables from baseline than those receiving placebo. Their ppFEV₁ increased by a mean (SD) of 13.1% (14.0%) in the omalizumab group compared with 9.2% (12.9%) in the placebo group (Table 3). Using ANCOVA, patients treated with omalizumab had a greater improvement in ppFEV₁ from baseline than those receiving placebo (LSM treatment difference [95% CI]: 3.0% [0.2%–5.7%]; *P* = .035; Fig 1A).

Absolute FEV₁ demonstrated similar results, with mean (SD) improvements of 215.8 (429.4) and 114.8 (385.9) mL in omalizumab- vs placebo-treated patients, respectively (Table 3; LSM treatment difference [95% CI]: 120.9 mL [30.6–211.2 mL]; *P* = .009; Fig 1B).

Mean (SD) FVC improvements of 224.7 (439.0) and 133.8 (338.8) mL were observed in omalizumab- and placebo-treated patients, respectively (Table 3). Using ANCOVA, FVC improvements were significantly greater in patients receiving omalizumab compared with those receiving placebo (LSM treatment difference [95% CI]: 101.5 mL [8.3–194.6 mL]; *P* = .033; Fig 1C).

Eosinophil Counts

Mean (SD) reductions in eosinophil counts of -125.0 (234.2) and -17.2 (228.6) cells/ μ L were observed in omalizumab- and placebo-treated patients, respectively (Fig 2A). Analysis of covariance demonstrated that reductions in eosinophils were

Table 1
Summary of the Studies Included in This Analysis^a

Study name/number	Type	Duration, weeks	Analysis timepoint, week	Disease severity	Overall patients, n	Adolescents included in this analysis, n		
						Omalizumab	Placebo	Total
Study 008 ²⁰	Double blind	28	16 ^{b,c}	Severe allergic asthma	525	20	21	41
Study 009 ²⁵	Double blind	28	16 ^{b,c}	Moderate-to-severe allergic asthma	546	18	17	35
Study 011 ²²	Double blind	32	16 ^{b,c}	Severe allergic asthma	246	12	9	21
SOLAR ²⁶	Double blind	28	28 ^{b,c}	Concomitant moderate-to-severe allergic asthma and persistent allergic rhinitis	405	20	17	37
INNOVATE ²⁷	Double blind	28	28 ^{b,c}	Severe persistent asthma	419	6	6	12
ALTO ²⁹	Open label	24	24 ^b	Moderate-to-severe persistent allergic asthma	1899	85	44	129
ETOPA ²⁸	Open label	52	27, ^b 53 ^c	Moderate-to-severe allergic asthma	312	19	7	26
EXTRA ²¹	Double blind	48	28, ^b 32 ^c	Severe allergic asthma	850	23	16	39
Total						203	137	340

Studies 008, 009, and 011 included a steroid-reduction phase.

^aAll studies were phase 3, randomized, multicenter studies.

^bAnalysis timepoint for spirometry.

^cAnalysis timepoint for blood eosinophil counts.

significantly greater with omalizumab (−42.0 cells/ μ L) compared with placebo (43.9 cells/ μ L), with an LSM treatment difference (95% CI) of −85.9 cells/ μ L (−137.1 to −34.6 cells/ μ L; $P = .001$; Fig 2B).

Discussion

Using pooled data from 8 placebo-controlled trials of omalizumab, these findings are the first to our knowledge to demonstrate that omalizumab significantly improves lung function in adolescents with moderate-to-severe uncontrolled asthma compared with placebo. Improvements were noted across all lung function measures, with improvements of 3%, 121 mL, and 102 mL being observed in ppFEV₁, FEV₁, and FVC, respectively. Lung function improvements were associated with reductions in peripheral eosinophil counts of 86 cells/ μ L. These results taken together are consistent with reduced airway obstruction, improved lung functioning, and reduced airway inflammation, and they highlight the potential therapeutic effect of omalizumab in patients whose condition remains uncontrolled on current therapies.

Studies on omalizumab specifically in adolescent populations have been sparse, but analyses from the Prospective Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab (PROSPERO)²⁴ and the STELLAIR¹⁴ study demonstrated efficacy of omalizumab in adolescents. Results from these analyses extend on previous findings for adolescents enrolled in the real-world study, PROSPERO.²⁴ Similar improvements in pre-bronchodilator FEV₁ of 170 and 121 mL were observed in adolescents in PROSPERO and this pooled analysis, respectively.²⁴ The results obtained for ppFEV₁ (3%) were also comparable with those observed in studies by Busse et al²⁰ and Soler et al,²⁵ which comprised adults and adolescents aged 12 to 75 years. Although the effect of omalizumab on adolescent vs adult populations was not investigated in this study, findings from PROSPERO and STELLAIR showed slightly larger increases in FEV₁²⁴ and larger reductions in exacerbations¹⁴ in the adolescent population compared with the adult population, emphasizing the need for early treatment intervention in the disease course to produce better clinical outcomes.

Although this analysis demonstrated significant improvements in lung function in adolescents treated with omalizumab compared with placebo, considerable variation is seen within the literature regarding the definition of a clinically meaningful improvement in lung function in children and adolescents.^{31–34} An investigational study by Santanello et al³¹ showed that the minimal patient-perceivable improvement corresponded to an increase in FEV₁ of 10% (0.23 L) in 281 patients with asthma. However, the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines for interpretation of spirometry stipulate that an

improvement of at least 12% plus a difference of at least 200 mL in pre- and postbronchodilator FEV₁ is required.³² Although a between-treatment difference in FEV₁ of 100 to 200 mL has also been described as clinically important by the National Institutes of Health,³² other sources have reported a between-treatment difference in FEV₁ of 5%³³ or improvements of at least 15%³² from pre- to postbronchodilator ppFEV₁ as being clinically meaningful. The changes in FEV₁ and FVC reported in the current analysis are consistent with the ATS/ERS guidelines,³² and ppFEV₁

Table 2

Baseline Demographics and Clinical Characteristics

Demographic characteristics	Omalizumab (n = 203)	Placebo (n = 137)
Mean (SD) age, years	14.1 (1.7)	14.1 (1.7)
Male, n (%)	128 (63.1)	86 (62.8)
Mean (SD) height, cm	162.3 (10.1)	162.5 (10.6)
Race, n (%)		
White	156 (76.8)	97 (70.8)
Black	26 (12.8)	31 (22.6)
Asian	3 (1.5)	1 (0.7)
Other	18 (8.9)	8 (5.8)
Clinical characteristics		
Mean (SD) BMI, kg/m ² ^a	22.7 (5.9)	23.2 (5.6)
ppFEV ₁ , n (%)		
≥80%	48 (23.6)	27 (19.7)
60%–79%	101 (49.8)	65 (47.4)
<60%	52 (25.6)	45 (32.8)
Mean (SD) FVC, L ^b	3.5 (0.9)	3.4 (1.0)
Exacerbation history in previous year, n ^c (%)		
≤1	18 (8.9)	15 (10.9)
2–3	22 (10.8)	18 (13.1)
>3	9 (4.4)	6 (4.4)
IgE level, IU/mL		
Mean (SD)	304.6 (214.7)	294.0 (198.7)
Median (min, max)	257.0 (30, 1118)	245.0 (20, 815)
Absolute eosinophil count, cells/ μ L ^d		
Mean (SD)	396.9 (287.8)	387.0 (224.4)
Median (min, max)	348.4 (60, 2250)	365.0 (31, 1130)
Eosinophil count, cells/ μ L, n (%)		
<300	40 (19.7)	32 (23.4)
≥300	56 (27.6)	52 (38.0)

Abbreviations: BMI, body mass index; FVC, forced vital capacity; IgE, immunoglobulin E; max, maximum; min, minimum; ppFEV₁, percent predicted forced expiratory volume in 1 second; SD, standard deviation.

^aMissing values/not collected (placebo, n = 7).

^bMissing values/not collected (omalizumab, n = 22; placebo, n = 7).

^cExacerbation was defined in all studies as worsening of asthma symptoms requiring treatment with systemic corticosteroids or doubling of the patient's baseline inhaled corticosteroid dose in studies 008 and 009 and SOLAR.

^dMissing values/not collected (omalizumab, n = 107; placebo, n = 53).

Table 3
Summary of Lung Function Measurements at Baseline and EOS

	ppFEV ₁ , %		Absolute FEV ₁ , L/mL		FVC, L/mL ^a	
	Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab	Placebo
Mean (SD) FEV ₁ or FVC at baseline	n = 203 68.4 (15.2)	n = 137 66.7 (15.7)	n = 203 2.7 (0.7)	n = 137 2.6 (0.8)	n = 181 3.5 (0.9)	n = 130 3.4 (1.0)
Mean (SD) FEV ₁ or FVC at EOS ^b	n = 148 81.5 (16.6)	n = 116 75.7 (17.1)	n = 179 2.9 (0.7)	n = 131 2.8 (0.8)	n = 161 3.7 (0.9)	n = 125 3.6 (1.0)
Mean (SD) change from baseline	n = 148 13.1 (14.0)	n = 116 9.2 (12.9)	n = 179 215.8 (429.4)	n = 131 114.8 (385.9)	n = 161 224.7 (439.0)	n = 124 133.8 (338.8)

Abbreviations: EOS, end of study; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ppFEV₁, percent predicted forced expiratory volume in 1 second; SD, standard deviation.

^aFVC data were not collected from ETOPA.

^bEOS was defined as the assessment closest to week 28; for the 3 studies (008, 009, 011) that included a steroid-reduction phase, EOS was the last nonmissing observation in the double-blind core treatment steroid-stable phase (week 16). EOS for SOLAR, INNOVATE, and EXTRA was week 28; for ALTO, week 24; and ETOPA, week 27.

improvements in the treatment arm met the minimally perceptible difference of 10% described by Santanello et al,³¹ suggesting that the observed lung function improvements may be clinically relevant. The clinical relevance of the changes in FEV₁ observed in the current study are further supported by the improvements in exacerbation rates and asthma symptom scores observed in patients with asthma after omalizumab treatment.^{20–22,25–27} These findings should be interpreted with caution, because placebo-treated patients also experienced increases in ppFEV₁, FEV₁, and FVC. Although the improvements were significantly smaller than those experienced by omalizumab-treated patients, the potential exists that improved adherence to ICS is partially responsible for the effects seen.

Measurement of lung function after treatment of asthma is clinically important because poor lung function is a prognostic factor for clinical outcomes in children with asthma.³⁵ Patients displaying significant airflow obstruction, for instance, are twice as likely to develop an exacerbation and exhibit reduced FEV₁ in adulthood than patients with normal lung function.^{13,35,36} Furthermore, in a small proportion of patients with asthma, irreversible airway obstruction may develop through abnormal development of lung function in childhood and an accelerated decline in lung function in adulthood.^{13,36} Together with the findings from PROSPERO,²⁴ findings from these studies suggest that treatment with omalizumab may contribute to improvements in maximally attained FEV₁ in adolescence. In this study, the effect of omalizumab on improving rather than preserving lung function is reflected in the observations that placebo-treated patients demonstrated significantly smaller changes in ppFEV₁, which takes into consideration a patient's height and age, than omalizumab-treated patients. Longer-term studies are required to determine how this impacts lung function in adulthood.

Eosinophilic airway inflammation also has been associated with lung function decline,³⁷ with treatment of eosinophilic airway inflammation using corticosteroids being shown to reduce the rate of lung function decline from 34 to 20 mL/year over 4 years of treatment.³⁸ Omalizumab specifically targets Th2 inflammation and has been shown to reduce eosinophil counts in blood and sputum^{39–41} and to reduce interleukin 5 secretion by mononuclear cells.⁴¹ Within this pooled analysis, we observed a reduction in eosinophil counts after omalizumab treatment, which paralleled the pattern of lung function improvement. This suggests that lung function improvement may be at least partially induced as a result of inflammatory modulation. Indeed, this hypothesis is supported by the observation that eosinophil-derived proteins, such as major basic protein and eosinophil peroxidase, have been shown to induce transient bronchoconstriction in primates,⁴² and eosinophil cationic protein and eosinophil-derived neurotoxin increase after methacholine challenge and correlate with a late decline in FEV₁ in atopic patients with asthma.⁴³

The main strengths of this analysis include the trial design of the included studies (randomized, multicenter) and the larger sample size (n = 203 and n = 137 for omalizumab- and placebo-treated patients, respectively) available for analysis compared with the individual studies. Pooling patient data from clinical trials of omalizumab allowed greater insight into lung function in adolescent populations than has been reported previously. However, the current analysis was also subject to inherent limitations associated with the post hoc nature of the analyses and limitations associated with integrating data from 8 studies that had important differences in design, patient populations, background medication, treatment duration, lung function tests performed, and data extraction procedures, which could have impacted outcomes. Two of the included studies were open label; although they were placebo controlled,

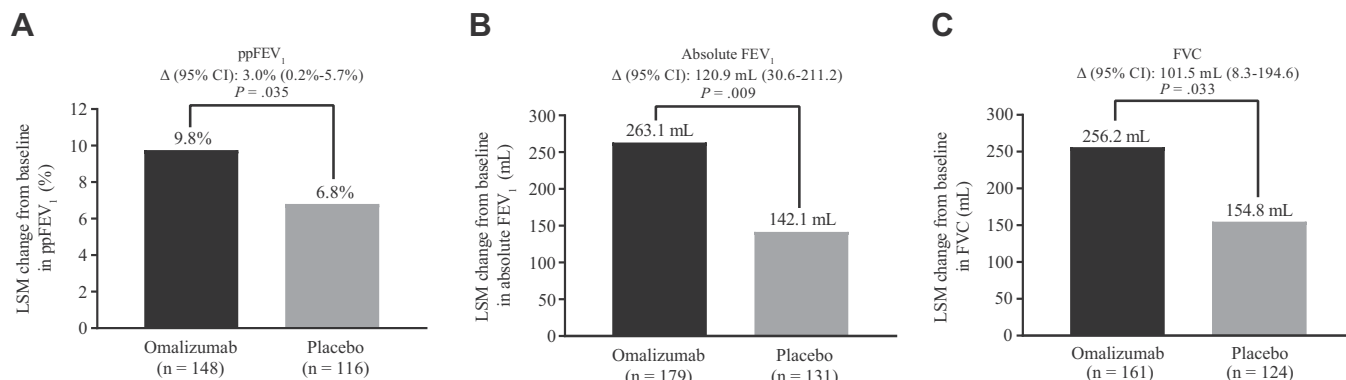


Figure 1. Change from baseline in (A) percent predicted (pp) forced expiratory volume in 1 second (FEV₁), (B) absolute FEV₁, and (C) forced vital capacity (FVC) based on least squares means (LSM).

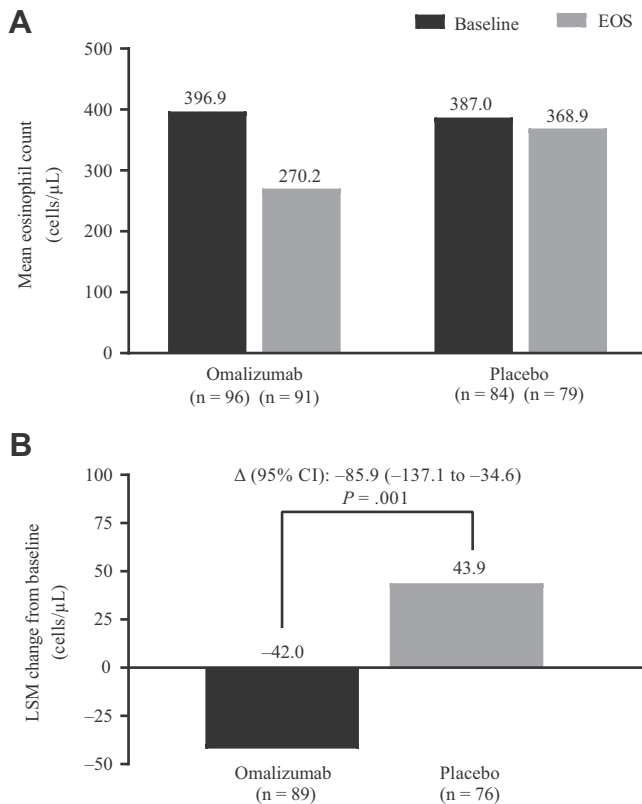


Figure 2. Eosinophil counts by (A) baseline and end of study (EOS), and (B) least squares mean (LSM) change from baseline.

the lack of blinding potentially permits bias. All included studies were performed between 2001 and 2005; because asthma management has changed in that time, the impact of omalizumab on lung function in patients treated with current asthma management protocols is unknown. This analysis only assessed lung function changes at end of study from baseline. Therefore, whether lung function continued to improve or whether the improvements in lung function noted in this analysis were maintained over time are unknown. This study did not examine factors that contribute to lung function improvements. Further analyses may identify patient populations who are more likely to achieve clinically relevant lung function improvements with omalizumab use. Furthermore, no statistical analysis examining the association between lung function improvements with reductions in airway inflammation was performed, and the mechanism of lung function improvements related to reductions in airway inflammation remains speculative. This should be explored further by performing a multivariable regression analysis.

In conclusion, the results of this post hoc pooled analysis demonstrate that omalizumab significantly improves lung function in adolescents with moderate-to-severe uncontrolled asthma compared with placebo. The significant improvements in lung function observed in patients receiving omalizumab emphasize the potential effect of omalizumab in patients whose condition remain uncontrolled on current therapies and the need to optimize treatment early in the disease course.

Data Sharing Statement

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (<https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx>).

For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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