

Original article

Omalizumab in children with inadequately controlled severe allergic (IgE-mediated) asthma

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Abstract**Background:**

Many children with severe persistent allergic (IgE-mediated) asthma remain inadequately controlled despite treatment with high-dose inhaled corticosteroids (ICS) plus a long-acting β_2 -agonist (LABA).

Research and design methods:

This pre-specified analysis of a randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of omalizumab in children (6–<12 years) with perennial allergen sensitivity, and history of asthma exacerbations and symptoms despite treatment with ICS (fluticasone $\geq 500 \mu\text{g} \cdot \text{day}^{-1}$ or equivalent) plus a LABA. Patients received omalizumab (75–375 mg once or twice a month by subcutaneous injection, as determined from dosing tables) or placebo over 52 weeks (24-week fixed-steroid then 28-week adjustable-steroid phases).

Results:

Out of 246 randomized patients (omalizumab, $n = 166$; placebo, $n = 80$), efficacy was analysed in 235 (omalizumab, $n = 159$; placebo, $n = 76$). Over the 24-week fixed-steroid phase, omalizumab reduced the rate of clinically significant asthma exacerbations (worsening symptoms requiring doubling of baseline ICS dose and/or systemic steroids) by 34% versus placebo (0.42 vs 0.63, rate ratio 0.662; $P = 0.047$). Over 52 weeks, the exacerbation rate was reduced by 50% ($P < 0.001$). Omalizumab had an acceptable safety profile, with no statistically significant ($P < 0.05$) differences in adverse events observed between omalizumab and placebo.

Conclusion:

Add-on omalizumab is well-tolerated and reduces exacerbations in children (6–<12 years) with severe persistent allergic asthma, inadequately controlled despite high-dose ICS plus a LABA. It should be noted that the sample size was not based on providing statistical power in the severe subgroup, and no corrections were made for multiple comparisons; however, outcomes consistently favoured omalizumab.

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Introduction

The high prevalence of paediatric asthma in Europe places a burden on children, their families and society¹. The prevalence of severe asthma symptoms has recently been estimated to range from 3.8% (Asia-Pacific region and Northern and Eastern Europe) to 11.3% (North America) in 13- to 14-year-olds and 3.2% (Asia-Pacific region and Northern and Eastern Europe) to 9.5% (Oceania) in 6- to 7-year-olds². Severe asthma results in a higher incidence of symptoms and a greater risk of asthma exacerbations, compared with mild-to-moderate disease^{3,4}. A European survey showed that only 5.8% of children (mean age [SD], 8.8 [4.1] years) with asthma met all of the Global Initiative for Asthma (GINA) 1995 criteria⁵ for asthma control despite currently available therapies⁴.

Asthma exacerbations are associated with loss of lung function⁶, hospital admissions⁷, and time lost from work and school^{8,9}. They are frequently treated with oral corticosteroids (OCS), which, if used in multiple bursts over a period of years, can result in serious side-effects such as reduced bone mineral accretion and increased risk of osteopenia¹⁰. OCS use has also been associated with arterial hypertension, diabetes, hypothalamic–pituitary–adrenal axis suppression, obesity, cataracts, glaucoma, skin thinning leading to cutaneous striae and easy bruising, and muscle weakness¹¹. Although rare, withdrawal of OCS can elicit adrenal failure⁵.

Severe asthma in adults and children is associated with persistent symptoms and poor response to therapy¹². In adults, combinations of inhaled corticosteroids (ICS) and long-acting β_2 -agonists (LABAs) are effective in many patients, but 38% of patients in one study remained inadequately controlled despite their use¹³. Another study showed that, despite treatment with high-dose ICS plus a LABA (and some additional controller medications) over 90% of patients required an emergency room visit, almost 50% required hospitalization, and over 98% of patients required OCS bursts (approximately four per patient) in the previous year¹⁴. In children, although asthma control can be improved by intensifying treatment, enhancing adherence, improving inhaler technique or altering the child's environment, at least 50% of children with severe asthma are poorly controlled despite multiple controller medications^{15,16}. In children receiving ICS, particularly at high doses, evidence of adrenal suppression can be found¹⁷. Additionally, adrenal crises have been reported in children treated with excessively high ICS doses¹⁸; however, these have not been observed in clinical trials⁵. Although LABAs are commonly used as add-on therapy in children whose asthma is insufficiently controlled by medium doses of ICS or as single dose therapy before vigorous exercise⁵, the benefit versus risk involved is not well documented in children¹⁹. LABAs have been associated with hospitalization in children, and there is conflicting evidence regarding their effect on exacerbation rates²⁰.

Individuals with asthma have a greater rate of decline in forced expiratory volume in 1 second (FEV₁) than those without asthma^{21,22}. However, in children, given the relatively short duration of their asthma history compared with adults, FEV₁ values are often normal during periods of disease stability²³, and most children with asthma have FEV₁ values close to normal^{22,24}. In a cohort study of moderate-to-severe asthma children, reported mean percent predicted FEV₁ values in children with mild, moderate and severe asthma were 95.2%, 90.2% and 83.8%, respectively (i.e. percent predicted FEV₁ still exceeded 80% in many children with severe asthma)²⁵.

The majority of children with asthma are atopic²⁶, and mean serum immunoglobulin E (IgE) is often particularly high in children with severe asthma²⁷, providing a

particularly strong rationale for investigating anti-IgE therapy in this population.

Omalizumab is a humanized anti-IgE antibody that has been previously approved for the treatment of adults and adolescents (≥ 12 years) with moderate-to-severe (USA) or severe (European Union [EU]) allergic (IgE-mediated) asthma^{28,29}. In the EU, the indication has recently been extended to include children (6–<12 years) with severe allergic (IgE-mediated) asthma. The EU indication stipulates that to be eligible for omalizumab therapy, patients aged 12 years and over should have reduced lung function (FEV₁ <80% of predicted), but this is not a requirement in children. The efficacy and safety of omalizumab have been demonstrated in adults and adolescents^{14,30–37}. A randomized, double-blind, placebo-controlled study of omalizumab in 334 children (6–12 years) with well controlled moderate-to-severe allergic asthma has also shown a similar efficacy and safety profile of omalizumab in children³⁸.

A recent 52-week study evaluated the efficacy and safety of omalizumab in children with inadequately controlled, moderate-to-severe persistent allergic (IgE-mediated) asthma³⁹. To evaluate the efficacy and safety of omalizumab in children with severe allergic asthma, we report the results of a sub-analysis of this study.

Patients and methods

Study design and patients

This pre-specified subgroup analysis was conducted using data collected in a large randomized, double-blind, placebo-controlled, parallel-group study³⁹. Details of the original study have been published previously³⁹. Briefly, patients (6–<12 years) were recruited from approximately 90 centres in Argentina, Brazil, Canada, Colombia, Poland, South Africa and the USA. Patients had moderate-to-severe allergic (IgE-mediated) asthma, inadequately controlled despite treatment with regular ICS (fluticasone propionate [FP] dry powder inhaler $\geq 200 \mu\text{g} \cdot \text{day}^{-1}$ or equivalent) with or without other controller medications (Step 3 or 4 of the National Heart, Lung and Blood Institute [NHLBI] guidelines⁴⁰) and a documented history of inadequately controlled asthma, including exacerbations, within the previous 2 years. Patients entered a 1-week screening phase, followed by an 8-week run-in phase to optimize asthma treatment and establish baseline asthma control measurements. ICS and other asthma control medications could be adjusted during the first 4 weeks of the run-in; further dose adjustments were not permitted during the last 4 weeks of the run-in. Those who remained inadequately controlled were then randomized 2:1 to receive omalizumab or placebo for a 52-week treatment period, consisting of a 24-week fixed-steroid phase, and a 28-week adjustable-steroid

phase, during which ICS dose could be reduced by 25–50% once every 8 weeks if patients met strict reduction criteria. Omalizumab 75–375 mg was administered once or twice a month by subcutaneous injection, with the dose determined using dosing tables, based on the patient's body weight and baseline total serum IgE. The primary efficacy endpoint was the rate of clinically significant asthma exacerbations (defined below) over 24 weeks in this population. The study is registered at the ClinicalTrials.gov website (identifier: NCT00079937). The original study was conducted according to the ethical principles of the Declaration of Helsinki. The study and any amendments were reviewed and approved by the Independent Ethics Committees or Institutional Review Boards for each centre. Parents or legal guardians were informed of study procedures and medications and gave written informed consent.

Inadequately controlled severe asthma subgroup analysis

This report focuses on the subgroup of children with inadequately controlled severe asthma, despite receiving high-dose ICS ($\geq 500 \mu\text{g} \cdot \text{day}^{-1}$ FP or equivalent) and a LABA, with or without other controller medications, which corresponds to the omalizumab EU indication in adults and adolescents.

Efficacy and safety assessments

The primary outcome measure was the rate of clinically significant exacerbations (worsening of asthma symptoms requiring doubling of the baseline ICS dose [although it should be noted that this is no longer recommended in treatment guidelines⁵] and/or treatment with systemic corticosteroids for ≥ 3 days) during the 24-week fixed-steroid phase. The secondary outcome measure was the rate of clinically significant asthma exacerbations during the 52-week treatment period. Exploratory outcome measures included the percentage change from baseline in ICS dose at the end of the 28-week adjustable-steroid phase, the rate of clinically significant asthma exacerbations over the 28-week adjustable-steroid phase, the rate of clinically significant exacerbations over 52 weeks in patients with baseline percent predicted FEV₁ $< 80\%$ and $\geq 80\%$, and the physician's global evaluation of treatment effectiveness (GETE; a five-level evaluation of excellent, good, moderate, poor or worsening) at 52 weeks. Safety was monitored by recording adverse events (AEs), serious AEs (SAEs), vital signs and any clinically significant changes in laboratory values, including haematology and blood chemistry.

Statistical analysis

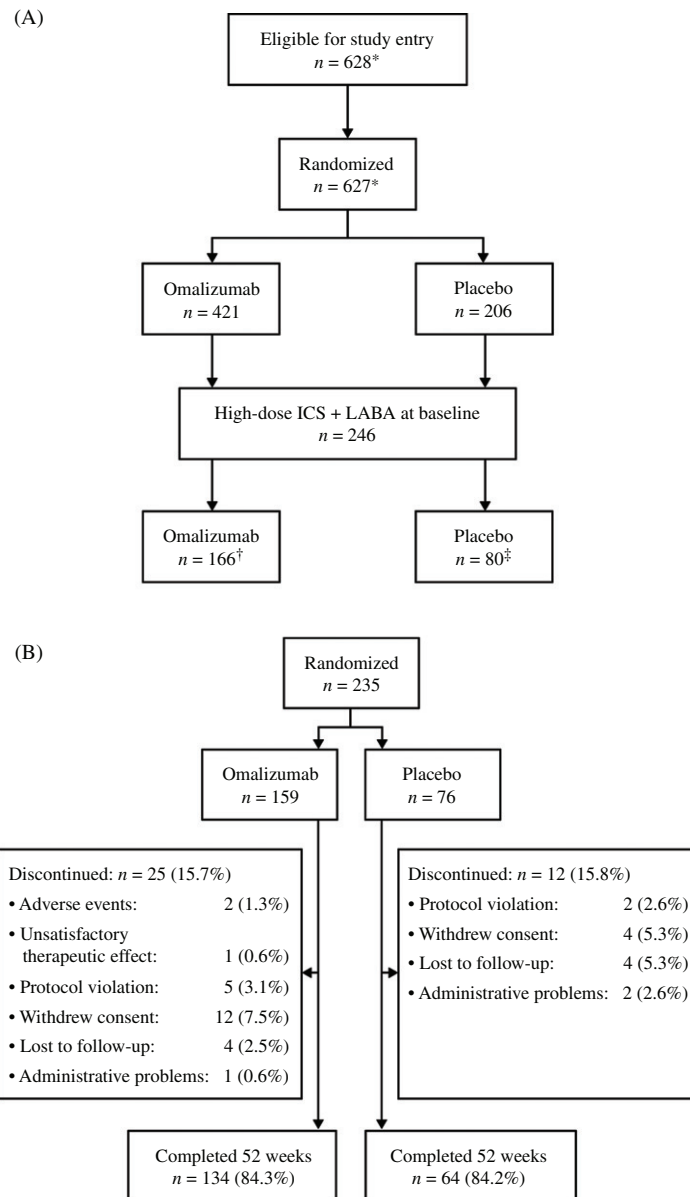
Efficacy analyses reported here are based on the EU modified intent-to-treat (EU mITT) population, consisting of all patients randomized to treatment, who were receiving at least high-dose ICS plus a LABA, after excluding patients from centres that were not compliant with Good Clinical Practice (GCP). The safety population consisted of all patients who were receiving at least high-dose ICS plus a LABA, received any study drug and had at least one post-baseline safety assessment. All statistical analyses were performed on SAS 8.2.

Statistical differences between group baseline characteristics were tested using the *F*-test, chi-squared test and Fisher's exact test, as appropriate. Rate of clinically significant asthma exacerbations over 24 and 52 weeks were compared between treatment groups using a two-sided test at $\alpha = 0.05$ with a generalized Poisson regression model. The rate ratio (RR) of exacerbations between the treatment groups and 95% confidence interval (CI) were obtained. For patients who discontinued early, exacerbation data were imputed for clinically significant exacerbations over 24 and 52 weeks (one added to the total number for patients who discontinued prematurely, unless they had an exacerbation ≤ 7 days prior to discontinuation). The percentage change from baseline in ICS dose was compared using the van Elteren test: a nonparametric test that compares treatments in the presence of blocking (an extension of Wilcoxon's rank-sum test)⁴¹; percent change in ICS dose for patients who discontinued before the 28-week adjustable-steroid phase was imputed as zero. The numbers of patients rated as excellent or good according to the physician's GETE were compared using the Cochran Mantel Haenszel test. Assessment of safety was based on the frequency of all AEs. Statistical differences between the frequency of AEs reported in the omalizumab and placebo groups were calculated using Fisher's exact test.

Results

Disposition and baseline characteristics

Of the 628 patients who received at least one dose of study drug in the original study (omalizumab $n = 421$; placebo $n = 207$ [one placebo-treated patient was not randomized but was included in the safety population]), 246 patients with severe asthma were included in the safety population of the current analysis (omalizumab $n = 166$; placebo $n = 80$; Figure 1A). From this population, 11 patients were excluded from the EU mITT due to non-compliance with GCP. The EU mITT population therefore consisted of 159 omalizumab-treated patients and 76 placebo-treated patients. Of these, 134 (84.3%) omalizumab-treated



*One patient in the placebo group was not randomized and therefore excluded from the ITT/mITT populations, but included in the safety populations.

†Includes seven patients who were subsequently excluded from the EU mITT due to study centre non-compliance with GCP.

‡Includes four patients who were subsequently excluded from the EU mITT due to study centre non-compliance with GCP.

Figure 1. Patient disposition in the original study (A) and in the inadequately controlled severe subgroup (B).

patients and 64 (84.2%) placebo-treated patients completed the study (Figure 1B).

Baseline demographic and clinical characteristics were generally well balanced between both treatment groups, although children in the omalizumab group were slightly older (Table 1). All patients were using ICS (mean [SD] dose of 744.0 [262.73] µg FP [or equivalent] per day) and

a LABA. Additionally, 135 patients (57.4%) were receiving anti-leukotriene therapy, six (2.6%) were receiving maintenance OCS and one (0.4%) was receiving theophylline. Patients had experienced a mean of 2.8 exacerbations in the year prior to study entry. At baseline, 181 patients (77.0%) had a daytime asthma symptom score ≥ 1 (scale: 0–4, where 0 = no symptoms; 4 = breathing

Table 1. Baseline demographic and clinical characteristics (modified intent-to-treat population).

	Omalizumab (n = 159)	Placebo (n = 76)	P value	Total (n = 235)
Mean (SD) age, years	9.1 (1.71)	8.6 (1.74)	0.049 ^a	9.0 (1.73)
Age distribution, n (%)				
6–9 years	76 (47.8)	47 (61.8)	0.044 ^b	123 (52.3)
10–11 years	83 (52.2)	29 (38.2)		112 (47.7)
Sex, n (%)				
Male	102 (64.2)	52 (68.4)	0.519 ^b	154 (65.5)
Female	57 (35.8)	24 (31.6)		81 (34.5)
Race, n (%)				
Caucasian	92 (57.9)	48 (63.2)	0.437 ^c	140 (59.6)
Black	50 (31.4)	21 (27.6)		71 (30.2)
Asian	0	1 (1.3)		1 (0.4)
Other	17 (10.7)	6 (7.9)		23 (9.8)
FEV ₁ , %-predicted	[n = 158]	[n = 76]		[n = 234]
Mean (SD)	81.8 (17.49)	82.6 (19.49)	0.776 ^a	82.1 (18.12)
FEV ₁ reversibility*, %	[n = 77]	[n = 36]		[n = 113]
Mean (SD)	29.4 (19.94)	25.1 (14.81)	0.25 ^a	28.0 (18.50)
Historical FEV ₁ reversibility†, %	[n = 82]	[n = 39]		[n = 121]
Mean (SD)	24.4 (14.06)	25.2 (10.93)	0.762 ^c	24.7 (13.09)
Mean (SD) serum total IgE, IU/ml	452.4 (328.30)	414.0 (305.63)	0.392 ^c	440.0 (320.99)

SD = standard deviation; FEV₁ = forced expiratory volume in 1 s; IgE = immunoglobulin E.

*Percentage increase over baseline within 30 min of rescue medication.

†Within the past 12 months.

^aF-test.

^bChi-squared test.

^cFisher's exact test.

problems at rest with major discomfort that limits routine activity) on ≥ 20 of the past 28 days, and 180 (76.6%) had night-time awakenings requiring rescue medication more than once per week.

Efficacy

Over the 24-week fixed-steroid phase, the rate of clinically significant asthma exacerbations was significantly lower in omalizumab-treated patients than in the placebo group (0.42 vs 0.63). The RR (omalizumab:placebo) (95% CI) was 0.662 (0.441, 0.995) equating to a 34% reduction with omalizumab ($P = 0.047$; Figure 2). Over the 52-week treatment period, the rate of clinically significant asthma exacerbations was 0.73 in omalizumab-treated patients and 1.44 in placebo-treated patients (RR [95% CI]: 0.504 [0.350, 0.725]; $P < 0.001$), equating to a reduction of 50% (Figure 3). During the 52-week treatment period, within the EU mITT population, 92% of clinically significant asthma exacerbations were treated with OCS.

The percentage reductions in ICS dose from baseline to the end of the 28-week adjustable-steroid phase were small and similar in both groups (omalizumab 2.5%; placebo 2.0%). Despite this, omalizumab further reduced asthma exacerbation rates over the 28-week adjustable-steroid phase. Over the 28-week adjustable-steroid phase (Weeks 25 to 52), the rate of clinically significant asthma exacerbations was 0.29 in omalizumab-treated patients and 0.77 in placebo-treated patients,

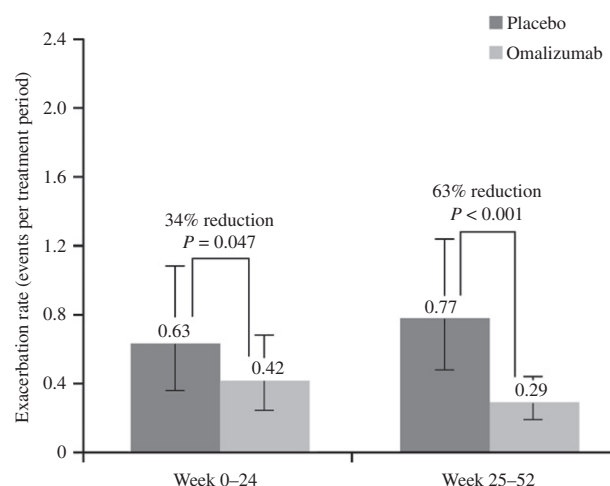


Figure 2. Clinically significant asthma exacerbation rates (95% confidence intervals) during the fixed-steroid phase (Weeks 0–24) and steroid-adjustment phase (Weeks 25–52) in patients with severe asthma treated with add-on omalizumab ($n = 159$) or placebo ($n = 76$) in the EU mITT.

(RR [95% CI]: 0.372 [0.243, 0.568]; $P < 0.001$), equating to a rate reduction of 63% (Figure 2).

Over 52 weeks, clinically significant exacerbations were significantly reduced in patients with baseline percent predicted FEV₁ $< 80\%$, (0.84 vs 1.64; RR [95% CI]: 0.512 [0.315, 0.833]; $P = 0.007$), and in those with baseline percent predicted FEV₁ $\geq 80\%$ (0.66 vs 1.35; RR [95% CI]: 0.488 [0.279, 0.854]; $P = 0.012$).

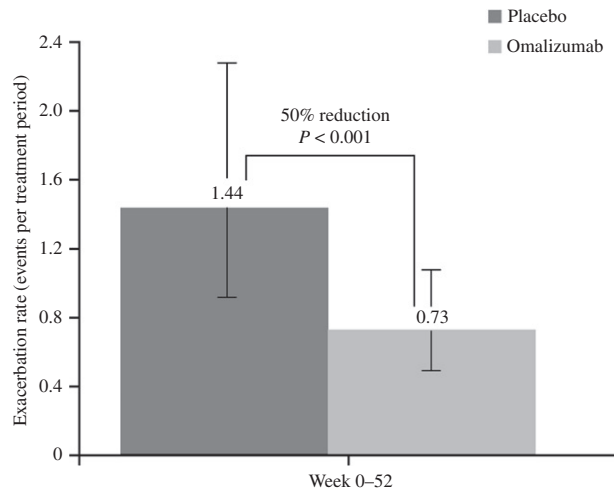


Figure 3. Clinically significant asthma exacerbation rates (95% confidence intervals) during the overall 52-week treatment period in patients with severe asthma treated with add-on omalizumab ($n = 159$) or placebo ($n = 76$) in the EU MITT.

Table 2. Incidence of adverse events (AEs) in the safety population.

	Omalizumab ($n = 166$)	Placebo ($n = 80$)	P value ^a
Patients with any AE, n (%)	155 (93.4)	76 (95.0)	0.779
Discontinued due to AE	2 (1.2)	0	1.000
Patients with SAEs, n (%)	6 (3.6)	8 (10.0)	0.073
Most frequent AEs*, n (%)			
Nasopharyngitis	49 (29.5)	20 (25.0)	0.545
Upper respiratory tract infection	40 (24.1)	28 (35.0)	0.094
Sinusitis	36 (21.7)	23 (28.8)	0.265
Pyrexia	31 (18.7)	7 (8.8)	0.059
Cough	27 (16.3)	12 (15.0)	0.854
Headache	24 (14.5)	12 (15.0)	1.000
Pharyngolaryngeal pain	21 (12.7)	10 (12.5)	1.000
Vomiting	19 (11.4)	10 (12.5)	0.834
Bronchitis	19 (11.4)	12 (15.0)	0.421
Viral upper respiratory tract infection	12 (7.2)	11 (13.8)	0.107
Pharyngitis, streptococcal	11 (6.6)	11 (13.8)	0.093

AE = adverse event; SAE = serious adverse event.

*Those occurring in $\geq 10\%$ of patients in either treatment group.

^aFisher's exact test.

More omalizumab-treated patients than placebo-treated patients were assessed as having an excellent or good response by the physician's GETE at 52 weeks (118 [74.2%] vs 42 [55.3%]; $P < 0.001$).

Safety

The mean exposure to omalizumab or placebo was 49.8 and 49.1 weeks, respectively, and 93% of patients completed at least 28 weeks on omalizumab. The overall incidence of AEs was similar in both groups (Table 2). Pyrexia was the

only AE that occurred with a frequency $\geq 5\%$ higher in the omalizumab group (18.7%) than in the placebo group (8.8%), but this difference was not statistically significant ($P = 0.059$). Of these reported incidences of pyrexia, three (two in patients receiving omalizumab and one in patients receiving placebo) were reported on the day of injection. Upper respiratory tract infection, sinusitis, viral upper respiratory tract infection, and streptococcal pharyngitis were more frequent in the placebo group ($\geq 5\%$) than in the omalizumab group.

The overall incidence of SAEs was lower in the omalizumab group than the placebo group (3.6% vs 10.0%). With the exception of two reports of pneumonia in the placebo group, SAEs were reported by only one patient per treatment group. One patient in the omalizumab group had an SAE that was suspected to be study-drug related (a moderate tic disorder). There were no deaths in either group. One omalizumab-treated patient discontinued the study due to an SAE (bronchitis, not suspected to be study-drug related).

No new safety concerns relating to AEs of particular clinical interest³⁷ were evident. No cases of serum sickness were reported. One omalizumab-treated patient had an anaphylactic reaction, but the event was attributed to administration of meperidine. In the original study³⁹, one patient in the placebo group also experienced an anaphylactic reaction (attributable to ingestion of nuts), but this patient did not meet the severe asthma criteria for the EU safety population. No malignancy was reported in omalizumab-treated patients. In the original study³⁹, one malignancy was reported in the placebo group, but this patient did not meet the severe asthma criteria for the EU safety population. Few patients experienced pre-specified changes in laboratory values (one omalizumab patient in the EU safety population had a transient low platelet count, but this had returned to normal on re-testing, with no associated bleeding disorders) and overall rates were similar in both groups. No thrombocytopenia was reported in the original study³⁹.

Discussion

This subgroup analysis of children with inadequately controlled severe allergic (IgE-mediated) asthma enrolled in a double-blind, placebo-controlled study showed that add-on omalizumab reduced clinically significant exacerbations by 34% compared with placebo over 24 weeks, and by 50% over 52 weeks. The greater reduction in exacerbations over the whole treatment period may be reflective of the emergence of full treatment effect with time, as suppressed free IgE levels down-regulate high-affinity IgE (FcεRI) receptors expressed on pro-inflammatory cells⁴². The definition of clinically significant exacerbations in this study is robust and compares favourably with other

major studies. These exacerbations represent clinically important events and, at the set thresholds, may develop into serious or even life-threatening events without prompt treatment.

The reduction in clinically significant asthma exacerbations in the severe subpopulation is consistent with those previously reported in children with moderate-to-severe asthma in the original study (31% and 43% over 24 and 52 weeks, respectively)³⁹, and with the annualized 38% reduction in adults and adolescents with severe persistent allergic (IgE-mediated) asthma³⁵. It is also consistent with those previously reported in children with well-controlled moderate-to-severe allergic asthma (32% over 16 weeks and 53% following a subsequent 8-week steroid-reduction phase)³⁸.

In the severe subpopulation in this analysis, the mean baseline percent predicted FEV₁ (82.1%) is consistent with that previously reported for severe asthma in this age group (83.8%)²⁵. In adults with severe asthma, annualized reduction in exacerbations with omalizumab in patients with percent predicted FEV₁ $\geq$ 80% at baseline were significant (31%; $P = 0.0003$)³⁵, but of a lower magnitude than those seen in children with percent predicted FEV₁ $\geq$ 80% over 52 weeks in the current study (51%; $P = 0.012$). In the current analysis, exacerbations were reduced by a similar magnitude, irrespective of whether baseline percent predicted FEV₁ was above or below 80% (51% and 49% reductions, respectively).

The safety profile of omalizumab in this analysis reflects that seen in the larger population in the original study³⁹. The overall incidence of AEs was similar in both omalizumab and placebo groups, SAEs were less frequent in the omalizumab group, and no new safety concerns were evident.

The reduction in asthma exacerbations and favourable safety and tolerability profile that are associated with omalizumab in the present analysis are important, as there are limited options available to improve asthma control in children with severe asthma who are already receiving at least high-dose ICS and a LABA. Reduction in exacerbations may benefit the patient both in terms of the risks associated with the exacerbation itself, and the risks associated with using OCS in their treatment. Routine use of OCS is not recommended in children, due to the adverse effects associated with prolonged use, and repeated use of short courses of OCS has been shown to reduce bone mineral accretion in children¹⁰.

The plateau effect in ICS dose is well recognized in asthma guidelines. GINA guidelines state that "The preferred treatment at Step 4 is medium or high-dose ICS plus LABA; however, in most patients the increase from medium to high-dose ICS provides relatively little additional benefit"⁵. Despite an ICS dose of ≥ 500 μ g/day FP (or equivalent), more than double the maximum approved dose in children, plus a LABA and other controller

medications (e.g. 57% were receiving anti-leukotriene therapy), asthma symptoms of patients in this study remained inadequately controlled during the run-in. The addition of omalizumab to the treatment regimen of these patients increased symptom control in terms of exacerbations, suggesting a real treatment benefit in patients uncontrolled by maximum doses of ICS, in whom further increases of ICS dose may not improve asthma control.

A number of limitations of the present analysis should be noted. Although these analyses were pre-specified, the sample size was not based on providing statistical power in the severe subgroup, as was the case for the primary objective of the original study. As the effect of omalizumab therapy seen in this severe subgroup was similar to that observed in the core study population³⁹, despite the reduced power of the study, it is reasonable to assume the results are a real effect of omalizumab. Significant differences that favoured omalizumab were still seen in most efficacy outcomes. In addition, as no corrections were made for multiple comparisons, it is possible that significant differences may have arisen due to chance; however, the consistent differences that favoured omalizumab for a variety of outcomes indicates that this is unlikely. Finally, the doubling of baseline ICS dose is no longer recommended in treatment guidelines, and this criterion, compared with current guidelines, may have allowed the inclusion of more exacerbation episodes. Nevertheless, in this severe subgroup examined in this study, most exacerbations were treated with OCS.

Conclusion

The present sub-group analysis shows that omalizumab has an acceptable safety and tolerability profile and reduces asthma exacerbations in children with inadequately controlled severe allergic (IgE-mediated) asthma. Omalizumab may provide an important new means of improving control of severe asthma and reducing the risk of exacerbations in children.

Transparency

Declaration of funding

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Declaration of financial/other relationships

M.K. has no relevant financial interests to disclose. J.H. has disclosed that he has received research support from Merck, GSK, Novartis, Shire, Boehringer Ingelheim, Medimmune, Circassa and Stallergene. He has acted as a consultant for GSK, Novartis, Merck, CSL Behring, Allergilab and Nycomed, and has been part of Speaker Bureau for Merck, Novartis, King, CSL Behring and GSK. E.G. has disclosed that she has served

on the speakers' bureau and has received research support from Novartis; A.F.T., C.F.V. and M.B. have disclosed that they are all employees and shareholders of Novartis.

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References

- Sennhauser FH, Braun-Fahrlander C, Wildhaber JH. The burden of asthma in children: a European perspective. *Paediatr Respir Rev* 2005;6:2-7
- Lai C, Beasley R, Crane J, et al. Global variation in the prevalence and severity of asthma symptoms: Phase Three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2009;64:476-83
- Fitzpatrick AM, Gaston BM, Erzurum SC, et al. Features of severe asthma in school-age children: atopy and increased exhaled nitric oxide. *J Allergy Clin Immunol* 2006;118:1218-25
- Rabe KF, Vermeire PA, Soriano JB, et al. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J* 2000;16:802-7
- Global Initiative for Asthma. Global strategy for asthma management and prevention. Issued January 1995 (NIH Publication No. 02-3659); updated 2002, 2003, 2004, 2005, 2006, 2007, 2008. Available at: www.ginasthma.org [Last accessed 26 February 2010]
- Bai TR, Vonk JM, Postma DS, et al. Severe exacerbations predict excess lung function decline in asthma. *Eur Respir J* 2007;30:452-6
- Marion RJ, Creer TL, Reynolds RV. Direct and indirect costs associated with the management of childhood asthma. *Ann Allergy* 1985;54:31-4
- Diette GB, Markson L, Skinner EA, et al. Nocturnal asthma in children affects school attendance, school performance, and parents' work attendance. *Arch Pediatr Adolesc Med* 2000;154:923-8
- Silverstein MD, Mair JE, Katusic SK, et al. School attendance and school performance: a population-based study of children with asthma. *J Pediatr* 2001;139:278-83
- Kelly HW, Van Natta ML, Covar RA, et al. Effect of long-term corticosteroid use on bone mineral density in children: a prospective longitudinal assessment in the childhood Asthma Management Program (CAMP) study. *Pediatrics* 2008;122:e53-61
- National Heart, Lung and Blood Institute/National Asthma Education and Prevention Program (NHLBI/NAEPP 2007). Expert Panel Report 3: guidelines for the diagnosis and management of asthma, 2007. NIH Publication No. 07-4051. Available at: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm [Last accessed 22 December 2008]
- Bacharier LB, Boner A, Carlsen KH, et al. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy* 2008;63:5-34
- Bateman E, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004;170:836-44
- Niven R, Chung KF, Panahloo Z, et al. Effectiveness of omalizumab in patients with inadequately controlled severe persistent allergic asthma: an open-label study. *Respir Med* 2008;102:1371-8
- Bush A, Hedlin G, Carlsen KH, et al. Severe childhood asthma: a common international approach? *Lancet* 2008;372:1019-21
- Chippes BE, Szeffler SJ, Simons FE, et al. Demographic and clinical characteristics of children and adolescents with severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2007;119:1156-63
- Randell T, Donaghue KC, Ambler GR, et al. Safety of the newer inhaled corticosteroids in childhood asthma. *Paediatr Drugs* 2003;5:481-504
- Todd GR, Acerini CL, Ross-Russell R, et al. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Arch Dis Child* 2002;87:457-61
- Main C, Shepherd J, Anderson R, et al. Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta2 agonists for the treatment of chronic asthma in children under the age of 12 years. *Health Technol Assess* 2008;12:1-174,iii-iv
- Bisgaard H. Effect of long-acting beta2 agonists on exacerbation rates of asthma in children. *Pediatr Pulmonol* 2003;36:391-8
- Lange P, Parner J, Vestbo J, et al. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998;339:1194-200
- Paull K, Covar R, Jain N, et al. Do NHLBI lung function criteria apply to children? A cross-sectional evaluation of childhood asthma at National Jewish Medical and Research Center, 1999-2002. *Pediatr Pulmonol* 2005;39:311-17
- Spahn JD, Cherniack R, Paull K, et al. Is forced expiratory volume in one second the best measure of severity in childhood asthma? *Am J Respir Crit Care Med* 2004;169:784-6
- Bacharier LB, Strunk RC, Mager D, et al. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. *Am J Respir Crit Care Med* 2004;170:426-32
- Bacharier L, Mager D, Lemanske RJ, et al. Classifying asthma severity in children: is measuring lung function helpful? *J Allergy Clin Immunol* 2002;109:S266
- Arbes Jr SJ, Gergen PJ, Vaughn B, et al. Asthma cases attributable to atopy: results from the Third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 2007;120:1139-45
- Borish L, Chipps B, Deniz Y, et al. Total serum IgE levels in a large cohort of patients with severe or difficult-to-treat asthma. *Ann Allergy Asthma Immunol* 2005;95:247-53
- Genentech Inc: Omalizumab (Xolair®) full prescribing information (US), July 2007. Available at: www.gene.com/gene/products/information/immunological/xolair/insert.jsp [Last accessed 25 September 2009]
- European Medicines Agency (EMA): Omalizumab (Xolair®) full prescribing information (EU), 2009. Available at: <http://www.emea.europa.eu/humandocs/PDFs/EPAR/Xolair/emea-combined-h606en.pdf> [Last accessed 25 September 2009]
- Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001;108:184-90
- Solè M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001;18:254-61 (erratum in *Eur Respir J* 2001;18:739-40)
- Holgate ST, Chuchalin AG, Hébert J, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy* 2004;34:632-8
- Ayres JG, Higgins B, Chilvers ER, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. *Allergy* 2004;59:701-8
- Vignola AM, Humbert M, Bousquet J, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis (SOLAR). *Allergy* 2004;59:709-17
- Bousquet J, Cabrera P, Berkman N, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy* 2005;60:302-8
- Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005;60:309-16

37. Corren J, Casale TB, Lanier B, et al. Safety and tolerability of omalizumab. *Clin Exp Allergy* 2009;39:788-97
38. Milgrom H, Berger W, Nayak A, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics* 2001;108:E36
39. Lanier R, Bridges T, Kulus M, et al. Omalizumab for the treatment of exacerbations in children with uncontrolled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol* 2009;124:1210-16
40. NHLBI. The NAEPP Expert Panel Report: guidelines for the diagnosis and management of asthma-update on selected topics. NIH Publication No 02-5075, 2002
41. van Elteren PH. On the combination of independent two-sample tests of Wilcoxon; *Bull Int Stat Inst* 1960;37:351-61
42. MacGlashan Jr DW, Bochner BS, Adelman DC, et al. Down-regulation of FcεRI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol* 1997;158:1438-45