

Efficacy and safety of omalizumab in children and adolescents with moderate-to-severe asthma: A systematic literature review

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ABSTRACT

Background: There are limited pediatric data about the use of omalizumab, especially the effectiveness and safety of omalizumab in the real-world management of allergic asthma.

Objective: The objective of this study was to summarize the safety and efficacy of omalizumab in both randomized clinical trials (RCT) used for U.S. Food and Drug Administration registration and real-world studies (RWS) based on clinical care of children with moderate-to-severe asthma.

Methods: Studies that evaluated omalizumab use in patients <18 years old and with asthma, published between January 2003 and October 2016, were retrieved from medical literature data bases. Assessed outcomes included the following: exacerbation rates, spirometric indices, changes in asthma medication use, asthma control, patient-reported outcomes, and health care resource utilization.

Results: A total of five RWS were identified; outcomes reported were compared with three omalizumab RCTs. Overall, the mean rate of annual exacerbations was significantly lower after 6 months to 2 years of treatment with omalizumab in both RCTs and RWS. In two RCTs and three RWS, inhaled corticosteroid use was significantly reduced in patients who used omalizumab. Similar reductions in the use of rescue medication were also observed in the RCTs and RWS on omalizumab. Real-world evidence demonstrated improvement in forced expiratory volume in the first second of expiration (% predicted) in patients treated with omalizumab as well as significant improvement in the level of asthma control observed over 1 year. There also was evidence that omalizumab treatment reduced health care resource utilization, including fewer hospitalizations, emergency department visits, and unscheduled medical visits. Safety outcomes in all five RWS showed no new safety signals and demonstrated that omalizumab was well tolerated.

Conclusion: Overall, RCT evidence strongly supported omalizumab efficacy and safety as add-on treatment in children 6 to 11 years old with moderate-to-severe persistent allergic asthma. RWS data confirmed these findings in an extended patient population of children and adolescents that is more generalizable to the actual day-to-day management of these patients.

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Asthma is the most common chronic disease in children,¹ which affects >6.2 million children and adolescents in the United States.² An allergic component has been observed in ~80% of these patients,

with evidence of immunoglobulin E (IgE) antibodies to a relevant airborne allergen.³ Despite aggressive use of conventional medical therapy, including inhaled corticosteroids (ICS), long-acting β -adrenergic agonists, and leukotriene antagonists, large population-based surveys showed that up to 60% of pediatric patients' asthma remains poorly controlled.^{4,5} Patients with uncontrolled asthma account for the majority of direct costs attributable to asthma, with disproportionately high numbers of asthma-related physician visits, emergency department care, and hospitalizations.⁶ In addition, uncontrolled asthma is associated with substantial indirect costs for children and their caregivers, which results in school absenteeism and loss of parental work productivity.^{5,7}

Until recently, few therapeutic options were available for children with treatment-refractory asthma. Omalizumab (Xolair; Genentech, San Francisco, CA), a humanized monoclonal antibody directed at IgE, was initially

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approved by the U.S. Food and Drug Administration (FDA) in 2003 for adolescents and adults with moderate-to-severe persistent allergic asthma (AA) uncontrolled by ICS. In July 2016, the FDA also approved omalizumab for children ages 6 to 11 years with poorly controlled asthma.⁸ The FDA approval was supported by two randomized, double-blind, placebo controlled trials in a total of 926 pediatric patients (ages 6–11 years) with moderate-to-severe persistent, IgE-mediated asthma.^{9,10}

As with all new treatment options, it is important to evaluate and/or validate the findings from clinical trials conducted in controlled clinical settings with effectiveness and safety in the “real-world” management of a disease. Compared with clinical trial data, studies of real-world evidence more closely describe how a medication will perform in more-diverse populations over longer periods of time and provide information regarding outcomes that are often not part of clinical trial protocols. Although such studies of omalizumab in adults exist,¹¹ there have been few studies in the pediatric population and no summary analyses. As such, this review article summarized data regarding the effectiveness and safety of omalizumab in both randomized clinical trials (RCT) used for FDA registration and real-world studies (RWS) based on clinical care in children with moderate-to-severe asthma.

Literature Review Search

A review of the literature that evaluated the use of omalizumab in patients with asthma who were <18 years old was conducted of studies published from January 2003 to October 2016. Data base sources searched were MEDLINE (via PubMed), EMBASE (Elsevier B.V., Amsterdam, The Netherlands), and the Cochrane Central Library of Controlled Trials (Wiley Online Library, Hoboken, NJ). Given the objective of the review, the Population, Intervention, Comparators, Outcomes, and Study Design criteria¹² were broadly applied to identify relevant studies to the research questions in this study. Although the population of interest for the review was pediatric patients, the search criteria was set as <18 years of age to avoid inadvertent exclusions of studies that included pediatric patients and adolescents.

The intervention of interest was omalizumab (search terms “omalizumab” or “Xolair”). Search filters included English language and human studies, with no geographic limitations. Study designs of interest were prospective and retrospective cohort studies. Unpublished studies, nonsystematic reviews, editorials, commentaries, and letters were excluded. In the context of this review, an RWS was considered to be a study that maintained the patient in his or her normal treatment setting, with no randomization to intervention or placebo. Five RWS, conducted in the United

States, France, Japan, Germany, and the United Kingdom, were identified in the review and included for further evaluation.^{13–17} These studies included one retrospective observational analysis¹³ and four prospective cohort studies^{14–17} (Table 1). The clinical end points used in these studies included asthma exacerbation rates, spirometric indices, changes in the use of asthma medications (controller and rescue), and levels of asthma control (Table 2). Overall, outcome measures were similar in the RWS to those used in the omalizumab RCTs.

RESULTS

Asthma Exacerbation Rates

Common measures of effectiveness and asthma control in the RCTs and RWS included asthma exacerbations, medication usage, and spirometric indices. The impact of omalizumab on reducing the rate of exacerbations was evaluated in all three RCTs^{9,10,19} and three of the 5 RWS,^{14,15,16,18} underscoring its clinical relevance to patients and caregivers. Definitions of exacerbations varied considerably across the RCTs and RWS (Table 3); however, in general, exacerbations were considered to consist of a worsening of symptoms severe enough to warrant a course of oral corticosteroids (OCS) or an increase in the dose of ICS. Both RCTs and RWS showed that asthma exacerbations were significantly reduced after 6 months to 2 years of treatment with omalizumab (Table 4).^{9,10,14,15,18}

Spirometry

In the RCTs, there were no significant differences in forced expiratory volume in 1 second (FEV₁) between the omalizumab and placebo groups from weeks 24 to 48.^{9,19} However, in the studies based on real-world evidence, statistically significant improvement in FEV₁ (% of predicted) was observed in three of four studies^{13,14,17} (Table 5). The FEV₁ improved significantly as early as 16 weeks in a subset of patients who were <12 years of age and who required OCS for maintenance.¹⁷

Use of Asthma Medications

In two RCTs, ICS dose reduction was significantly greater with omalizumab treatment compared with placebo.^{9,19} In Milgrom *et al.*,⁹ 55% of children treated with omalizumab and who were already well controlled with ICS therapy were able to discontinue ICS therapy completely versus 39% of children in the placebo group ($p = 0.004$). Similar findings were observed in the three RWS,^{14,15,17,18,20} although the magnitude of the steroid-sparing effects varied and the statistical tests were generally not conducted for this outcome (Table 6). In the retrospective analysis of 27 patients with severe asthma published by Campbell *et al.*,¹³ 23%

Table 1 Overview of identified studies

Study, y	Key Inclusion Criteria	Randomized Patients, n	Age, y*	Serum IgE Level, IU/mL*	Treatment Dose Frequency	Study Design
RCTs						
Milgrom <i>et al.</i> , ⁹ 2001	6–12 y of age; moderate-to-severe AA (≥ 1 y duration); total serum IgE level, 30–1300 IU/mL; well controlled for ≥ 3 mo with ICS (168–420 $\mu\text{g/day}$ BDP equivalent) and a bronchodilator as needed; FEV ₁ (pred) $\geq 60\%$	N = 334: 225 OMA, 109 Pbo	OMA, 9.4 (5–12); Pbo, 9.5 (6–12)	OMA, 348 (20–1269); Pbo, 323 (29–1212)	0.016 mg/kg/ IgE in IU/mL for 4 wk	RCT: 4–6-wk run-in phase (all children switched to an equivalent BDP dose, adjusted to maintain asthma control achieved with previous ICS, before randomization to OMA or Pbo); 16-wk stable-steroid phase (constant ICS dose); 12-wk steroid-reduction phase (8-wk steroid-reduction phase to the minimum effective dose and then maintained for the final 4 wk)
Lanier <i>et al.</i> , ¹⁰ 2009	6 to <12 y of age; moderate-to-severe AA; total serum IgE level, 30–1300 IU/mL; uncontrolled with ICS (≥ 200 $\mu\text{g/day}$ FP or equivalent and a bronchodilator as needed) and a history of severe exacerbation within the previous 2 y	N = 627: 421 OMA, 206 Pbo	OMA, 8.7 $\pm$ 1.7; Pbo, 8.4 $\pm$ 1.7	OMA, 476.0 $\pm$ 339.3; Pbo, 456.9 $\pm$ 335.8	75–375 mg according to dosing table every 2–4 wk	RCT: 8-wk run-in phase (asthma control optimized; ICS/controller medication could be adjusted during the first 4 wk only; patients who remained symptomatic during the last 4 wk were randomized to OMA or Pbo); 24-wk stable-steroid phase (constant ICS dose); 28-wk steroid-adjustable phase (ICS dose reduced only if patients met strict predefined criteria)

Table 1 Continued

Study, y	Key Inclusion Criteria	Randomized Patients, n	Age, y*	Serum IgE Level, IU/mL*	Treatment Dose Frequency	Study Design
Busse <i>et al.</i> , ¹⁹ 2011	6–20 y of age; persistent AA (>1 y duration); total serum IgE level, 30–1300 IU/mL; uncontrolled asthma indicated by persistent symptoms or hospitalization and/or unscheduled urgent care in the previous 6–12 mo	N = 419: 208 OMA, 211 Pbo	OMA, 10.9 ± 3.6; Pbo, 10.8 ± 3.4	NA	0.016 mg/kg/ IgE in IU/ mL for 4 wk	RCT: 4-wk run-in phase: (asthma control optimized before randomization to OMA or Pbo) followed by 60-wk treatment period (ongoing treatment adjustments were made to achieve good asthma control)
RWS						
Campbell <i>et al.</i> , ¹³ 2008	6–18 y of age; mild, moderate, or severe persistent asthma	OMA severe, n = 27; moderate/severe, n = 34; mild, n = 65	OMA severe, 13 ± 3; moderate/severe, 11 ± 3; mild, 10 ± 3	OMA severe, 405; moderate/severe, 353; mild, 117	Based on total IgE level and weight of the child by using standard dosing table recommendations	Retrospective observational study: retrospective analysis conducted in a pediatric allergy and immunology clinic
Steiss <i>et al.</i> , ¹⁶ 2012	8–17 y of age; OMA treatment due to severe allergic bronchial asthma	OMA, n = 10	OMA, 12.4 (8–17)	1373 ± 845.1	Dose was determined by the total IgE level	Prospective cohort study: Patients selected for treatment with OMA because of severe allergic bronchial asthma despite treatment with inhaled steroids, and/or LABA, LTRA, and/or systemic steroids; the regimen was monitored based on the total IgE measurements in patients treated with OMA over a period of 12–60 mo

Table 1 Continued

Study, y	Key Inclusion Criteria	Randomized Patients, n	Age, y*	Serum IgE Level, IU/mL*	Treatment Dose Frequency	Study Design
Brodie <i>et al.</i> , ¹⁷ 2012	5–16 y of age; severe asthma maintained on oral prednisolone for ≥ 3 mo before commencing trial	OMA total, $n = 34$; ages < 12 y, $n = 15$; ages ≥ 12 y, $n = 19$	NA (5–16)	NA	75–375 mg according to the dosing table every 2–4 wk	Prospective cohort study: 16 wk; therapeutic trial of OMA was performed as part of routine clinical management; other asthma therapies were not altered during the trial
Deschildre <i>et al.</i> , ¹⁴ 2013, and Deschildre <i>et al.</i> , ¹⁸ 2015	6–18 y of age; severe AA; partially (18%) or poorly (82%) controlled asthma; mean ICS dose of 703 $\mu\text{g}/\text{day}$ FP or equivalent	OMA, $n = 104$	11.9 (6–18)	1125 (934–1315)	75–375 mg according to the dosing table, every 2–4 wk	Multicenter observational survey: 104 wk (baseline to week 52, then to week 104); multicenter survey conducted in pediatric pulmonology and allergy tertiary care centers
Odajima <i>et al.</i> , ¹⁵ 2015, and Odajima <i>et al.</i> , ²⁰ 2017	6–15 y of age; uncontrolled severe AA despite receiving ICS and ≥ 2 controller medications	OMA, $n = 38$	10.7 ± 2.46	335.5 (33.6–1050.0)	75–375 mg according to the dosing table, every 2–4 wk	Prospective cohort study: 2-wk screening period; 24-wk treatment period (16-wk fixed phase and 8-wk adjustable phase); 16 wk after final dosing; extension study

IgE = immunoglobulin E; RCT = randomized controlled trial; AA = allergic asthma; ICS = inhaled corticosteroid; BDP = beclomethasone dipropionate; FEV₁ = forced expiratory volume in 1 second; pred = predicted; OMA = omalizumab; Pbo = placebo; FP = fluticasone propionate; NA = not available; RWS = real-world study; LABA = long-acting β -adrenergic agonist; LTRA = leukotriene antagonist.

*Data are presented as mean $\pm$ standard deviation or as mean (range).

Table 2 Summary of end points and assessments in identified studies

	RCTs			RWS				
	Milgrom <i>et al.</i> , ⁹ 2001	Lanier <i>et al.</i> , ¹⁰ 2009	Busse <i>et al.</i> , ¹⁹ 2011	Campbell <i>et al.</i> , ¹³ 2008	Deschildre <i>et al.</i> , ¹⁴ 2013/ <i>et al.</i> , ¹⁸ 2015	Odajima <i>et al.</i> , ¹⁵ 2015, and Odajima <i>et al.</i> , ²⁰ 2017	Steiss <i>et al.</i> , ¹⁶ 2012	Brodlie <i>et al.</i> , ¹⁷ 2012
Medication use								
OCS use					×			×
ICS use and/or dose	×	×	×	×	×	×		
SABA (“rescue medication”) use	×	×				×		
LABA use				×		×		
LTRA use				×		×		
Lung function								
FEV ₁	×			×	×	×		×
PEF	×		×			×	×	
FEV ₁ :FVC ratio				×	×			
Atopy								
Serum IgE levels	×			×		×	×	
Efficacy								
Exacerbations	×	×	×			×	×	
Level of control					×	×		
PROs (patient or physician reported)					×	×		
ACT or C-ACT			×	×		×		×
Symptom days			×					
Nocturnal clinical symptom score	×	×				×		
Total asthma symptom score						×		
Physician GETE	×	×						
Patient GETE	×	×						
Mean daily activity score						×		
Pediatric QoL questionnaire		×	×					
AQLQ		×				×	×	×

Table 2 Continued

	RCTs			RWS				
	Milgrom <i>et al.</i> , ⁹ 2001	Lanier <i>et al.</i> , ¹⁰ 2009	Busse <i>et al.</i> , ¹⁹ 2011	Campbell <i>et al.</i> , ¹³ 2008	Deschildre <i>et al.</i> , ¹⁴ 2013/ <i>et al.</i> , ¹⁸ 2015	Odajima <i>et al.</i> , ¹⁵ 2015, and Odajima <i>et al.</i> , ²⁰ 2017	Steiss <i>et al.</i> , ¹⁶ 2012	Brodie <i>et al.</i> , ¹⁷ 2012
Economic measures								
Health care resource utilization	×		×		×	×		
Safety								
AEs	×				×	×		
Discontinuation due to AE	×	×			×	×		
RCT = randomized controlled trial; RWS = real-world study; OCS = oral corticosteroid; ICS = inhaled corticosteroid; SABA = short-acting β -agonist; LABA = long-acting β -agonist; LTRA = leukotriene receptor antagonist; FEV ₁ = forced expiratory volume in 1 second; PEF = peak expiratory flow; FVC = forced vital capacity; IgE = immunoglobulin E; GINA = Global Initiative for Asthma; JPAC = Japanese Pediatric Asthma Program; PRO = patient-reported outcome; ACT = Asthma Control Test; C-ACT = Childhood Asthma Control Test; GETE = Global Evaluation of Treatment Effectiveness; QoL = quality of life; PAQLQ = Pediatric Asthma Quality of Life Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; AE = adverse event.								
*Reported in Ref. ²⁰								
#Health-related quality of life and/or ACT as stated in the text.								

Table 3 Study definitions of exacerbations

Study	Study-Reported Definition of Exacerbation
Milgrom <i>et al.</i> , ⁹ 2001	Required doubling of beclomethasone dose or systemic corticosteroids
Lanier <i>et al.</i> , ¹⁰ 2009	Worsening of asthma symptoms that required doubling of the baseline ICS dose and/or treatment with rescue systemic corticosteroids for ≥ 3 days
Busse <i>et al.</i> , ¹⁹ 2011	Required systemic glucocorticoids, hospitalization, or both
Deschildre <i>et al.</i> , ¹⁴ 2013, and Deschildre <i>et al.</i> , ¹⁸ 2015	Severe exacerbations: required systemic steroid bursts for ≥ 3 days
Odajima <i>et al.</i> , ¹⁵ 2015, and Odajima <i>et al.</i> , ²⁰ 2017	Worsening of asthma symptoms that required doubling of the maintenance ICS dose for ≥ 3 days and/or systemic corticosteroids
Steiss <i>et al.</i> , ¹⁶ 2012	Not defined

ICS = inhaled corticosteroid.

Table 4 Asthma exacerbations reported in RCTs and RWS

Study	Asthma Exacerbations		Timepoint, wk
	Placebo group or at baseline vs OMA group or at follow-up	<i>p</i> Value	
RCTs			
Milgrom <i>et al.</i> , ⁹ 2001	2.72 vs 0.42 per patient	<0.001*	28
Lanier <i>et al.</i> , ¹⁰ 2009	0.64 vs 0.45 per patient (31% reduction)	0.007#	24
Lanier <i>et al.</i> , ¹⁰ 2009	1.36 vs 0.78 per patient (43% reduction)	<0.001#	52
Busse <i>et al.</i> , ¹⁹ 2011	48.8 vs 30.3% with ≥1 exacerbation	<0.001§	48
RWS			
Deschildre <i>et al.</i> , ¹⁴ 2013	4.40 per patient during the previous year vs 1.25 per patient during the second year of treatment	<0.0001¶	52
Deschildre <i>et al.</i> , ¹⁸ 2015	1.25 vs 0.22 per patient	0.0001¶	52–104
Odajima <i>et al.</i> , ¹⁵ 2015	2.99 vs 0.92 per patient-year	<0.001	24
Steiss <i>et al.</i> , ¹⁶ 2012	Range of 2–6 per patient per year before therapy vs range of 0–3 per patient per year after 12 mo	NR	52

RCT = randomized controlled trial; RWS = real-world study; OMA = omalizumab; NR = not reported.

*By using the generalized van Elteren test stratified by treatment schedule (every 2 wk, every 4 wk).

#By using generalized Poisson regression.

§By using logistic regression.

¶By using the *t*-test for paired samples.

||By using the Wilcoxon signed-rank test for paired data.

were able to reduce their ICS doses from a high dose to a medium dose during omalizumab treatment.

Likewise, in an observational study by Deschildre *et al.*¹⁴ of patients with AA partially or poorly controlled at baseline, 46.7% of the patients achieved at least a 50% reduction in their ICS dose over 1 year (from mean 703 $\mu\text{g}/\text{day}$ fluticasone equivalent at baseline to 481 $\mu\text{g}/\text{day}$ at 52 weeks; $p < 0.0001$). This reduction in ICS use was maintained at the end of the second year (mean daily dose, 429 $\mu\text{g}/\text{day}$ at 104 weeks).¹⁸ In the prospective cohort study by Odajima *et al.*,¹⁵ the baseline ICS dose was not as high (mean, 469.7 $\mu\text{g}/\text{day}$

fluticasone equivalent); however, 10.5% of patients were still able to reduce or discontinue ICS during the 24-week treatment period, and this increased to 36.8% of the patients during the study extension period.²⁰ With regard to chronic use of OCS, two studies reported a significant steroid-sparing effect in patients treated with omalizumab.^{17,18} In the study by Deschildre *et al.*¹⁸ of children and adolescents with moderate-to-severe AA, six patients required continuous OCS therapy at study initiation; at the end of the 1-year treatment period, OCS was withdrawn in all patients. Brodlie *et al.*¹⁷ performed an observational study of

Table 5 Lung function tests

Study	FEV ₁ Measurement	Findings*	p Value
RCTs			
Milgrom <i>et al.</i> , ⁹ 2001	FEV ₁	Baseline, OMA vs Pbo: 1797.1 vs 1855.2 mL	NR
Busse <i>et al.</i> , ¹⁹ 2011	% of predicted FEV ₁	Wk 24, OMA vs Pbo: 1891.0 vs 1883.5 mL Baseline, OMA vs Pbo: 92.9 ± 18.7% vs 92.2 ± 17.6% Week 48, OMA vs Pbo: 92.6 ± 0.60% vs 91.7 ± 0.64% Difference, OMA vs Pbo at wk 48: 0.92 (95% CI, −0.81 to 2.64)	0.30
RWS			
Brodie <i>et al.</i> , ¹⁷ 2012	FEV ₁ in all patients	Baseline, 2100 mL (median)	0.1
	FEV ₁ in patients <12 y	At 16 wk, 2250 mL (median)	0.0058
Odajima <i>et al.</i> , ¹⁵ 2015	% of predicted FEV ₁	Baseline, 1800 mL (median)	NR
Odajima <i>et al.</i> , ²⁰ 2017		At 16 wk, 2100 mL (median)	
Deschildre <i>et al.</i> , ¹⁴ 2013	% of predicted FEV ₁	Baseline, 90.3 ± 19.3%	0.023
Deschildre <i>et al.</i> , ¹⁸ 2015		Wk 24, 89.7 ± 23.1% End of treatment, 89.2 ± 15.8% Baseline, 88% (95% CI, 83.8–92.2%) 1 y, 92.1% Mean improvement to 1 y, 4.9% (95% CI, 0.69, 9.19%)	
Campbell <i>et al.</i> , ¹³ 2008	% of predicted FEV ₁	2 y, 89.9% (95% CI, 86.7–93.0%) Before OMA, 71% ± 15% vs after OMA, 81% ± 15%	0.38 0.0004

FEV₁ = forced expiratory volume in 1 second; RCT = randomized clinical trial; OMA = omalizumab; Pbo = placebo; RWS = real-world study; NR = not reported; CI = confidence interval.

*Data are presented as mean or mean ± standard deviation except where noted otherwise.

children who required OCS maintenance therapy and reported a significant corticosteroid-sparing effect of omalizumab treatment: the median OCS dose was reduced from 20 to 5 mg/day ($p < 0.0001$).

Reductions in the use of rescue medication were also observed in the omalizumab studies. Although two of the RCTs reported a reduction in albuterol usage of ~1 puff per day from baseline,^{9,10} the comparison versus placebo was only statistically significant in Milgrom *et al.*⁹ (reduction of 1.1 puffs/day versus 0.94 puffs/day; $p = 0.004$). A similar reduction of 1.3 puffs/day (baseline, 2.8 puffs/day) in Lanier *et al.*¹⁰ was not significantly different from the placebo reduction of 1.0 puffs/day. Only one RWS reported rescue medication use. In the study by Odajima *et al.*,¹⁵ which included an asthma population that was more severe than that observed in the RCTs, treatment with omalizumab resulted in a significant reduction in rescue medication usage by week 24 (from 6.6 to 2.2 puffs/tablets per week).

Asthma Control

The level of asthma control was assessed in two RWS and not in the RCTs.^{18,20} In both studies, there was

significant improvement in the level of asthma control observed by investigators over 1 year. In Deschildre *et al.*,¹⁴ asthma control levels defined as good were improved from 0 to 67% of patients from entry to week 52; asthma control levels defined as poor were reduced from 82 to 8% of the patients in the same time period ($p < 0.0001$). At the end of the second year, only 5% of the patients had poor control and 80% had good control ($p = 0.17$).¹⁸ In the study by Odajima *et al.*,²⁰ asthma control levels defined as complete or well controlled were improved from 23.7 to 76.3% of patients from the start of the extension study to the end of the treatment period ($p < 0.001$ for the mean change in the Japanese Pediatric Asthma Control Program score).

Patient-Reported Outcomes

As shown in Table 2, a wide range of patient-reported outcomes were evaluated in the RCTs and RWS. In the RCTs, omalizumab treatment generally resulted in statistically significant improvement versus placebo in patient-reported outcomes that assessed

Table 6 Steroid use

Study	Measure of ICS Use	Placebo group vs OMA group, or Pre-OMA period vs follow-up period	p Value
RCTs			
Milgrom <i>et al.</i> , ⁹ 2001	Median change in ICS dose, % (baseline ICS dose of 267 $\mu\text{g}/\text{day}$ for placebo and 284 $\mu\text{g}/\text{day}$ for OMA)*	−66.7 vs −100%	0.001
	% patients with complete withdrawal of BDP	39 vs 55%	0.004
Lanier <i>et al.</i> , ¹⁰ 2009	Change in ICS dose, % (overall baseline ICS dose of 515.1 $\mu\text{g}/\text{day}$)#	2 vs −4%	0.053
Busse <i>et al.</i> , ¹⁹ 2011	Mean daily ICS dose, $\mu\text{g}/\text{day}$ *	771 mcg/day vs 663 $\mu\text{g}/\text{day}$ Difference of −109 $\mu\text{g}/\text{day}$ (14% dose reduction)	<0.001
RWS			
Campbell <i>et al.</i> , ¹³ 2008	% patients on high-dose ICS	82 vs 44% 23% of patients were able to reduce from high-dose to medium-dose ICS	NR
Brodie <i>et al.</i> , ¹⁷ 2012	Median daily OCS dose, mg/day in subanalysis of patients <12 y	Before OMA, 20 mg At 16 wk, 5 mg	<0.0001
Deschildre <i>et al.</i> , ¹⁴ 2013	Mean daily ICS dose, $\mu\text{g}/\text{day}$ #	Before OMA, 703 $\mu\text{g}/\text{day}$ At the end of 1 y, 481 $\mu\text{g}/\text{day}$ Difference of −212 $\mu\text{g}/\text{day}$ (30% dose reduction)§	<0.0001 from baseline to year 1
Deschildre <i>et al.</i> , ¹⁸ 2015	% of patients with $\geq 50\%$ reduction in the administered ICS dose	At the end of 2 y, 429.0 $\mu\text{g}/\text{day}$ At the end of 1 y, 46.7% At end of 2 y, 63.0%	NR
	% of patients with complete withdrawal of OCS	100% (6 of 6 patients who required maintenance OCS before OMA)	NR
Odajima <i>et al.</i> , ¹⁵ 2015	Mean daily ICS dose, $\mu\text{g}/\text{day}$ #	Before OMA, 469.7 $\mu\text{g}/\text{day}$ At 24 wk, 455.3 $\mu\text{g}/\text{day}$ At end of treatment, 405.3 $\mu\text{g}/\text{day}$ Difference of −64.5 $\mu\text{g}/\text{day}$ (13.2% dose reduction)	NR
Odajima <i>et al.</i> , ²⁰ 2017			

Table 6 Continued

Study	Measure of ICS Use	Placebo group vs OMA group, or Pre-OMA period vs follow-up period	p Value
	% patients with dose reduction or discontinued ICS	At 24 wk, 10.5% At end of treatment, 36.8%	NR

ICS = inhaled corticosteroid; OMA = omalizumab; RCT = randomized clinical trial; BDP = beclomethasone dipropionate; RWS = real-world study; NR = not reported; OCS = oral corticosteroid.
 *BDP equivalent.
 #Fluticasone propionate equivalent.
 §Publication reports –212 µg/day reduction, but calculating the reduction (703 – 481 µg/day) yielded a 222 µg/day reduction.

asthma symptoms and control, such as the Asthma Control Test, the Childhood Asthma Control Test, and the Global Evaluation of Treatment Effectiveness.^{9,10,19} Omalizumab also improved nocturnal symptoms and sleep (measured on the Nocturnal Asthma Symptom Score), but statistical significance versus placebo was not reached or not reported. The results of the RWS revealed similar findings with regard to patient-reported control of symptoms.^{13,17}

Health-related quality of life (QoL) was evaluated in only one RCT, which found no significant difference on the Pediatric Asthma Quality of Life Questionnaire between the omalizumab and placebo groups at week 24.¹⁰ The Pediatric Asthma Quality of Life Questionnaire measures the most troublesome functional problems for children and adolescents (ages, 7–17 years) due to their asthma. QoL was likewise evaluated in one RWS by using the mini-Asthma Quality of Life Questionnaire, a 15-item scale that measures functional impairments (score range, 1–7, in which a higher score indicates better QoL).¹⁷ Overall, all the patients experienced an improvement in QoL, which increased from a mean score of 3.5 at baseline to 5.2 at week 16 ($p < 0.0001$); a greater magnitude of improvement was seen in a subset of patients <12 years of age (Table 7). Improvements in QoL from baseline were also reported after 24 weeks of treatment in Odajima *et al.*,¹⁵ ($p < 0.001$, based on a Japanese asthma-specific QoL scale) and after treatment for 1 year in Germany (the QoL scale not reported).¹⁶

Health Care Resource Utilization

The impact of omalizumab treatment on pharmacoeconomic outcomes was assessed in two RCTs; in both trials, omalizumab treatment significantly reduced the number of missed school days over 28 to 48 weeks of treatment.^{9,19} Over a 28-week treatment period, the number of unscheduled medical visits due to asthma was signifi-

cantly lower in patients treated with omalizumab versus placebo (mean, 0.15 versus 5.35; $p = 0.001$).⁹ Similarly, the frequency of hospitalizations over a 48-week treatment period was significantly lower in patients treated with omalizumab versus patients treated with placebo (1.5 versus 6.3%; treatment difference –4.7% [95% confidence interval, –8.6 to –0.9%]; $p = 0.02$).¹⁹ A similar reduction in health care resource use was observed in the RWS. In the analysis of 10 patients with severe AA, no patient required hospitalization during treatment with omalizumab.¹⁶ During 1 year of treatment with omalizumab in patients with severe AA, the proportion of children who required hospitalization dropped from 44% (in the year before treatment) to 6.7%, and hospital admissions decreased by 88.5%.¹⁴ In the study by Odajima *et al.*,²⁰ the mean number of hospitalizations due to asthma was significantly reduced from 1.33 per patient-year to 0.29 per patient-year (78.2% reduction; $p < 0.001$). Likewise, emergency department visits were reduced by 32.4% (from 0.7 per patient per year), although the change was not statistically significant. It should be noted that the rate of health care resource use before omalizumab was higher in the RWS than in the RCTs, likely due to a more severe patient population, as well as potentially due to national differences in treatment practices.

Safety Outcomes

The prescribing information for omalizumab indicates that the most common adverse reactions in pediatric patients (6 to <12 years of age) in the clinical trials (which occurred in $\geq 3\%$ of patients who received omalizumab and more frequently than in patients treated with placebo) were nasopharyngitis, headache, pyrexia, upper abdominal pain, pharyngitis streptococcal, otitis media, viral gastroenteritis, arthropod bites, and epistaxis.²¹ Warnings and precautions for use include anaphylaxis, malignancy, symptoms resembling serum sickness, and eosinophilic condi-

Table 7 Patient-reported outcomes

Study	PRO Assessment	Results	p Value
RCTs			
Milgrom <i>et al.</i> , ⁹ 2001	Physicians' GETE	Rating of good at wk 24 OMA vs Pbo: 44.7% vs 32.7%	<0.001
		Rating of excellent at wk 24 OMA vs Pbo: 31.5% vs 16.3%	<0.001
	Patients' GETE	Rating of excellent or good at wk 24 "Virtually identical to physicians' GETE" (scores not reported)	<0.001
Lanier <i>et al.</i> , ¹⁰ 2009	Nocturnal Asthma Symptom score (0–4 scale)	Mean at baseline, OMA vs Pbo: 0.21 vs 0.25 Mean scores remained low but lower for OMA vs Pbo at all evaluations	NR
	Physicians' GETE excellent/good	Rating of excellent or good at wk 52 OMA vs Pbo: 79 vs 56%	<0.001
	Patients' GETE	Rating of excellent or good at wk 52 OMA vs Pbo: 80 vs 72%	<0.001
Busse <i>et al.</i> , ¹⁹ 2011	PAQLQ overall score (1–7 scale)	Least squares mean difference for OMA vs Pbo: 0.04	0.676
	Nocturnal Asthma Symptom score (0–4 scale)	Baseline: NR Wk 24: OMA vs Pbo: -0.63 ± 0.72 vs $-0.50 \pm 0.71^*$	0.114
	C-ACT score (0–27 scale)	Baseline, OMA vs Pbo: 20.5 ± 3.8 vs $20.7 \pm 3.9^*$ Wk 48, OMA vs Pbo: 23.0 ± 0.21 vs $22.2 \pm 0.21^*$ Difference for OMA vs Pbo at wk 48: 0.78 (95% CI, 0.21–1.35)	0.007
Busse <i>et al.</i> , ¹⁹ 2011	ACT score (5–25 scale)	Baseline, OMA vs Pbo: 20.3 ± 3.8 vs $20.3 \pm 3.1^*$ Wk 48, OMA vs Pbo: 22.5 ± 0.22 vs $22.3 \pm 0.22^*$ Difference for OMA vs Pbo at wk 48: 0.19 (95% CI, -0.42 to 0.79)	0.54
RWS			
Brodie <i>et al.</i> , ¹⁷ 2012	Mini-AQLQ score (1–7 scale)	Baseline: 3.5 (range, 1–8.4) (median) Wk 16: 5.9 (range, 3.2–9.9) (median)	<0.0001
		Patients: <12 y of age Baseline: 2.3 (range, 1–7.4.2) (median) Wk 16: 5.2 (range, 3.5–6.9) (median)	0.0078
Brodie <i>et al.</i> , ¹⁷ 2012	ACT score (5–25 scale)	Baseline: 12 (range, 6–24) (median) Wk 16: 20 (range, 12–26) (median)	0.0001
		Patients: <12 y of age Baseline: 11 (range, 6–15) (median) Wk 16: 18 (range, 12–26) (median)	0.00207

Table 7 Continued

Study	PRO Assessment	Results	p Value
Campbell <i>et al.</i> , ¹³ 2008	ACT score (% of maximum ACT score)	Before OMA vs after OMA: 51 vs 73%	<0.002
Odajima <i>et al.</i> , ¹⁵ 2015	Nocturnal sleep score	Baseline: 9.2 ± 9.8* Wk 24: 2.8 ± 6.4* Change, -6.4 ± 11.3; 95% CI, -10.1 to -2.7*	NR

PRO = patient-reported outcome; RCT = randomized clinical trial; GETE = Global evaluation of treatment effectiveness; OMA = omalizumab; Pbo = placebo; NR = not reported; PAQLQ = Pediatric Asthma Quality of Life Questionnaire; C-ACT = Childhood Asthma Control Test; RWS = real-world study; ACT = Asthma Control Test; mini-AQLQ = mini-Asthma Quality of Life Questionnaire; CI = confidence interval.
*Data are presented as mean ± standard deviation.

tions.²¹ A previously published meta-analysis of the three RCTs^{9,10,19} included in this review indicated that the frequency of adverse events was similar between omalizumab (76.3%) and placebo (74.2%), as was the frequency of serious adverse events (5.2 and 5.6%, respectively).²² There was no evidence of an increased risk of anaphylaxis, urticaria, hypersensitivity reactions, or malignancies.

Real-world experiences with omalizumab confirm the safety findings with omalizumab and did not identify new or unexpected safety findings. Across all five RWS,^{13,14,15,16,17,18,20} the patients tolerated omalizumab well. In the French study of 104 patients with severe AA, one or more adverse events during the first year were reported in 45.2% of patients; the most common reactions were injection-site pain (which resulted in treatment discontinuation in one patient) and local reactions.¹⁴ Serious adverse events that resulted in treatment discontinuation occurred in six patients (urticaria, *n* = 1; anaphylaxis, *n* = 1; systemic reactions, *n* = 4). In the second year, treatment was discontinued in 15 patients (of 73 patients who remained in the study through the second year); 8 patients discontinued use due to omalizumab adverse events (fatigue, *n* = 6; local reactions, *n* = 1; and weight gain, *n* = 1).¹⁸

In the prospective open-label study in Japan, most patients (94.7%) had one or more adverse event; the most common events were similar to those reported in the clinical trials (nasopharyngitis, upper respiratory tract infection, asthma, gastroenteritis).¹⁵ Serious adverse events occurred in six patients, all of whom required hospitalization.¹⁵ In the extension study,²⁰ all the patients had one or more adverse event. Serious adverse events occurred in 10 patients, which required hospitalization. Overall, there were no treatment discontinuations during the core study and the extension due to adverse events; there were no reports of anaphylaxis.^{15,20} No patients discontinued omalizumab due to adverse events in the studies by Steiss *et al.*¹⁶ or Brodlić *et al.*¹⁷

DISCUSSION

During the past 40 years, clinical research has relied on RCTs for evaluating new therapeutic interventions in human disease.²³ The study design of RCTs establishes internal validity by controlling for bias through randomization and the blinding process, critical for the objective evaluation of a new technology or treatment. However, RCTs lack external validity and often have limited generalizability to a setting and patient group outside of the strictly defined trial protocol.²³ In contrast, observational, or “naturalistic,” studies generally include individuals with a much wider range of demographic characteristics, concomitant treatments, and comorbid conditions that reflect patients treated in real-world settings.²⁴

Evidence from RCTs strongly supports the efficacy of add-on treatment with omalizumab in improving clinical outcomes in patients with uncontrolled asthma despite ICS therapy.^{9,10,19,22} The data from RWS confirmed and extended these findings to a patient population that more closely reflects the day-to-day management of health care providers who care for children with severe asthma.^{13,14,15,16,17,18,20} The RWS had longer durations of observation, and these longer periods of follow-up demonstrated that asthma exacerbations were reduced to an even greater degree than was observed in shorter-duration RCTs. These studies also validated the ability for patients treated with omalizumab to reduce their ICS usage.

One of the important limitations of RWS evidence was that, unlike the RCTs, the inclusion criteria often included both pediatric and adolescent patients, which meant that the comparison of results was not identical. Two studies, however, conducted subgroup analyses of the results in patients <12 years of age. Brodlić *et al.*¹⁷ found similar findings in the younger patients, with statistically significant reduction in OCS dose, QoL, and asthma control. Deschildre *et al.*,¹⁴ in contrast, found that patients <12 years

of age were slightly less likely to achieve asthma control compared with older patients. Other subgroup analyses reported found no difference in omalizumab effectiveness in patients on high-dose ICS at baseline (500 μ g/day fluticasone equivalent versus 200 μ g/day fluticasone equivalent) or in patients with IgE levels of >700 kU/L.^{14,15}

CONCLUSION

The totality of evidence supported the role of omalizumab in treatment-resistant AA in the pediatric population under heterogeneous conditions. Omalizumab meets a medical need, especially in the pediatric population, in which moderate-to-severe persistent AA can greatly impact the ability of a child to function on a daily basis, impact his or her QoL, and affect school attendance.⁵ The steroid-sparing effects of omalizumab are especially important in this population to minimize the dose-dependent adverse effects of long-term treatment.²⁵ Additional real-world longitudinal studies are needed to determine the optimal duration of omalizumab treatment to maintain the steroid-sparing effects without compromising asthma control.

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