

Original Article

“Real-life” Effectiveness Studies of Omalizumab in Adult Patients with Severe Allergic Asthma: Meta-analysis

Abdulaziz Alhossan, PharmD^{a,b}, Christopher S. Lee, PhD^c, Karen MacDonald, PhD^d, and Ivo Abraham, PhD^{a,d,e} Riyadh, Saudi Arabia; Tucson, Ariz; and Portland, Ore

What is already known about this topic? Omalizumab improves outcomes in patients with severe allergic asthma in randomized clinical trials.

What does this article add to our knowledge? Omalizumab, as add-on treatment to inhaled corticosteroid $\pm$ long-acting β_2 -agonists agents, improves outcomes in patients with severe allergic asthma under conditions of heterogeneity in patients, clinicians, sites, and treatment patterns in “real-life” studies.

How does this study impact current management guidelines? Omalizumab, as an add-on therapy, is an effective treatment for patients with severe allergic asthma who do not respond sufficiently to prior treatment.

BACKGROUND: After the approval of omalizumab for severe allergic asthma, a total of 25 studies have evaluated the effectiveness of omalizumab under “real-life” conditions of heterogeneity in patients, clinicians, sites, and treatment patterns.

OBJECTIVE: We conducted a meta-analysis to evaluate the effectiveness of omalizumab focusing on treatment response, lung function, quality of life, symptom control, corticosteroid use, and exacerbations and hospitalizations at 4-6, 12, and 24 months.

METHODS: We searched PubMed and Embase for real-life studies on omalizumab in severe asthma published up to 2015. Three effect size types were extracted: single-point proportions; mean $\pm$ SD of change relative to baseline as raw numbers and standardized as Cohen's d ; and changes in proportions of patients as relative risk. Random-effects meta-analyses were

performed to account for within- and between-study heterogeneity. Studies were weighted by the DerSimonian and Laird method.

RESULTS: Per data available at the 3 time points, omalizumab therapy was consistently associated with large proportions of patients classified as “good” to “excellent” treatment responders (Global Evaluation of Treatment Effectiveness scale); improvements in forced expiratory volume in 1 second, quality of life (Asthma-related Quality-of-Life Questionnaire scale), and asthma symptom control (Asthma Control Test scale); reductions in oral and inhaled corticosteroid (ICS) use; and reductions in exacerbations and hospitalizations.

CONCLUSIONS: This meta-analysis of noncontrolled studies documents the real-life pharmacotherapeutic effectiveness of omalizumab, as add-on treatment to ICS $\pm$ long-acting β_2 -agonists agents, in improving outcomes in patients with severe allergic asthma under conditions of heterogeneity in patients, clinicians, sites, and treatment patterns. The results mirror, complement, and extend the efficacy data from randomized controlled trials. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: Omalizumab; Allergic asthma; IgE; Meta-analysis; Effectiveness

^aCollege of Pharmacy, King Saud University, Riyadh, Saudi Arabia

^bCenter for Health Outcomes and Pharmacoeconomic Research, University of Arizona, Tucson, Ariz

^cSchools of Nursing and Medicine, Oregon Health and Science University, Portland, Ore

^dMatrix45, Tucson, Ariz

^eCollege of Pharmacy and College of Medicine, University of Arizona, Tucson, Ariz
This work was supported by the Arizona Postdoctoral Fellowship Program in Clinical Research in Human Therapeutics. No funding was received from the manufacturer of omalizumab, nor from any other sources.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication April 21, 2016; revised January 19, 2017; accepted for publication February 3, 2017.

Available online ■■

Corresponding author: Ivo Abraham, PhD, Center for Health Outcomes and Pharmacoeconomic Research, University of Arizona, 1295 N. Martin, Tucson, AZ 85721. E-mail: abraham@pharmacy.arizona.edu.
2213-2198

© 2017 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2017.02.002>

Asthma affects up to 16% of people worldwide, much of which is due to a significant increase in incidence over the past 4 decades.¹⁻³ In the absence of a cure, the main treatment goal is asthma control to improve respiratory function; prevent exacerbations, unscheduled outpatient and emergency department visits, and hospitalizations; reduce the need for oral and inhaled corticosteroid (ICS) therapy; and thus improve quality of life.^{2,4} Despite guidelines, the majority of patients are controlled suboptimally, especially those with severe asthma.^{5,6}

Abbreviations used

ACT- Asthma Control Test
 AQLQ- Asthma-related Quality-of-Life Questionnaire
 FEV₁- Forced expiratory volume in 1 second
 GETE- Global Evaluation of Treatment Effectiveness scale
 ICS- Inhaled corticosteroid
 OCS- Oral corticosteroid
 RR- Relative risk

Problematic severe asthma refers to asthma and asthma-like symptoms that remain uncontrolled despite high-intensity treatment, and comprises “difficult asthma” and “severe refractory asthma.”⁷ Difficult asthma is severe asthma due to factors unrelated to the disease such as patient noncompliance, psychosocial factors, functional breathing or vocal cord impairment, environment exposure, or undertreated comorbidities.⁷ It is estimated to affect 17.4% of adult patients with asthma.⁸ Severe asthma not associated with any of these factors is classified as severe refractory asthma. It is defined as the presence of poorly controlled asthma symptoms and/or frequent severe exacerbations despite high-intensity treatment, or to asthma that can only be controlled with systemic corticosteroids. The prevalence is estimated at 3.6% of adult patients with asthma.⁸

One target in asthma treatment is to control the endogenous antibodies associated with allergic reactions such as IgE antibodies.⁹ Omalizumab is a recombinant monoclonal anti-IgE antibody that inhibits IgE binding sites^{10,11} and thus the activation of mast cells and the release of inflammatory mediators.⁹ Omalizumab is used as an add-on treatment to long-acting β_2 -agonists and ICS.¹²

Phase III randomized clinical trials have shown omalizumab to improve asthma symptoms, reduce exacerbations, and improve quality of life.^{13,14} Efficacy and safety data from these and subsequent studies have been reviewed elsewhere.^{12,15-17} After regulatory approval, the “real-life” effectiveness of omalizumab under conditions of greater heterogeneity in patients, clinicians, and treatment regimens has been evaluated extensively. In a recent systematic review of 24 “real-life” effectiveness studies conducted worldwide and published between 2008 and 2015, we concluded that adjuvant omalizumab therapy is associated with improvements across the full spectrum of objective and subjective indicators that may extend up to 2 to 4 years.¹⁸ This systematic review presented an overview of the studies conducted, and the outcomes observed. These outcomes were presented as a range from lowest to highest, however, without any justification. Here we follow up on this review with a meta-analysis of these 24 studies—plus 1 study published after the submission of our review for a total of 25—to quantitatively evaluate the “real-life” effectiveness of omalizumab in adult patients.

MATERIALS AND METHODS

Search strategy

We searched the PubMed and Embase databases for relevant published studies using the keywords “allergic asthma,” “IgE,” “omalizumab,” “observational,” “effectiveness,” and “real-life.” The first report on the effectiveness of omalizumab was published in 2008; thus, the search was limited from January 1, 2007, to December 31, 2015 (ahead-of-print) publications. In addition, the reference list of each manuscript retained was searched to identify

other potential studies of relevance. Published conference abstracts were tracked for full publications. Studies included were those that were observational in design and included at least one metric of effectiveness in common with one or more additional studies and at a concurrent time point of exposure to omalizumab (eg, 4-6, 12, and/or 24 months). A total of 25 observational studies including 9213 patients across 32 countries¹⁹⁻⁴³ were identified, the 24 being included in our systematic review and 1 published after submission of our review.¹⁸

Data extraction

Each study was evaluated by at least 2 reviewers. We developed and pilot-tested a data extraction tool per standard meta-analysis methodology. Any discrepancies were reconciled among the reviewers or, if not reconciled, escalated to a third person.

Outcomes

Studies differed in the outcomes measured. In several studies, physicians were asked to rate the effectiveness of omalizumab using the Global Evaluation of Treatment Effectiveness (GETE) scale. This scale rates a patient's overall response to treatment as being excellent, good, moderate, poor, or worsening. A GETE of good or excellent was used in several studies as an index of responsiveness, and rationale for continuing omalizumab treatment, particularly after 4 months. Another common measure across multiple studies was the forced expiratory volume in 1 second (FEV₁), which is included in this meta-analysis as the percentage of expected. Subjective asthma-related quality of life was often assessed using the Asthma-related Quality-of-Life Questionnaire (AQLQ).⁴⁴ A change of 0.5 points on the 7-point AQLQ scale represents a clinically meaningful improvement in asthma-related quality of life. Asthma control was also frequently assessed using the Asthma Control Test (ACT),⁴⁵ a questionnaire with an overall score ranging from 5 (poorly controlled asthma) to 25 (well-controlled asthma). Also included in this meta-analysis were the proportion of patients requiring oral corticosteroids (OCS) or the amount of ICS required in beclomethasone equivalents as specified in the studies and matched each study's period of observation. Exacerbations were reported as the proportion of the sample that was exacerbation free and in annualized incidence rates. Asthma-related hospitalizations were reported in annualized incidence rates as well.

Statistical analysis

Our approach to this meta-analysis was guided by recommended analytic and reporting criteria.⁴⁶ Raw published/publically available data were extracted, verified in duplicate, and combined into a single database. Three effect size types were extracted from the literature. First, single-point estimates, such as the proportion of patients with a good or excellent GETE versus those without, were extracted as the number of successes versus total sample size. Second, mean improvements relative to a known baseline, such as improvements in FEV₁ or AQLQ, were extracted as mean change and the standard deviation of change or as raw pretreatment and posttreatment means and standard deviations. Standardized mean differences (Cohen's *d*)⁴⁷ were calculated as the primary metric for continuous measures; mean changes are also presented in the original metric for interpretability. Interpretation-wise, a Cohen's *d* of 0.2 is considered a small, 0.5 a medium, and 0.8 a large effect. Third, the number of patients requiring OCS at a given time point relative to the number of patients requiring OCS before the initiation of omalizumab was calculated in the metric of relative risk (RR).

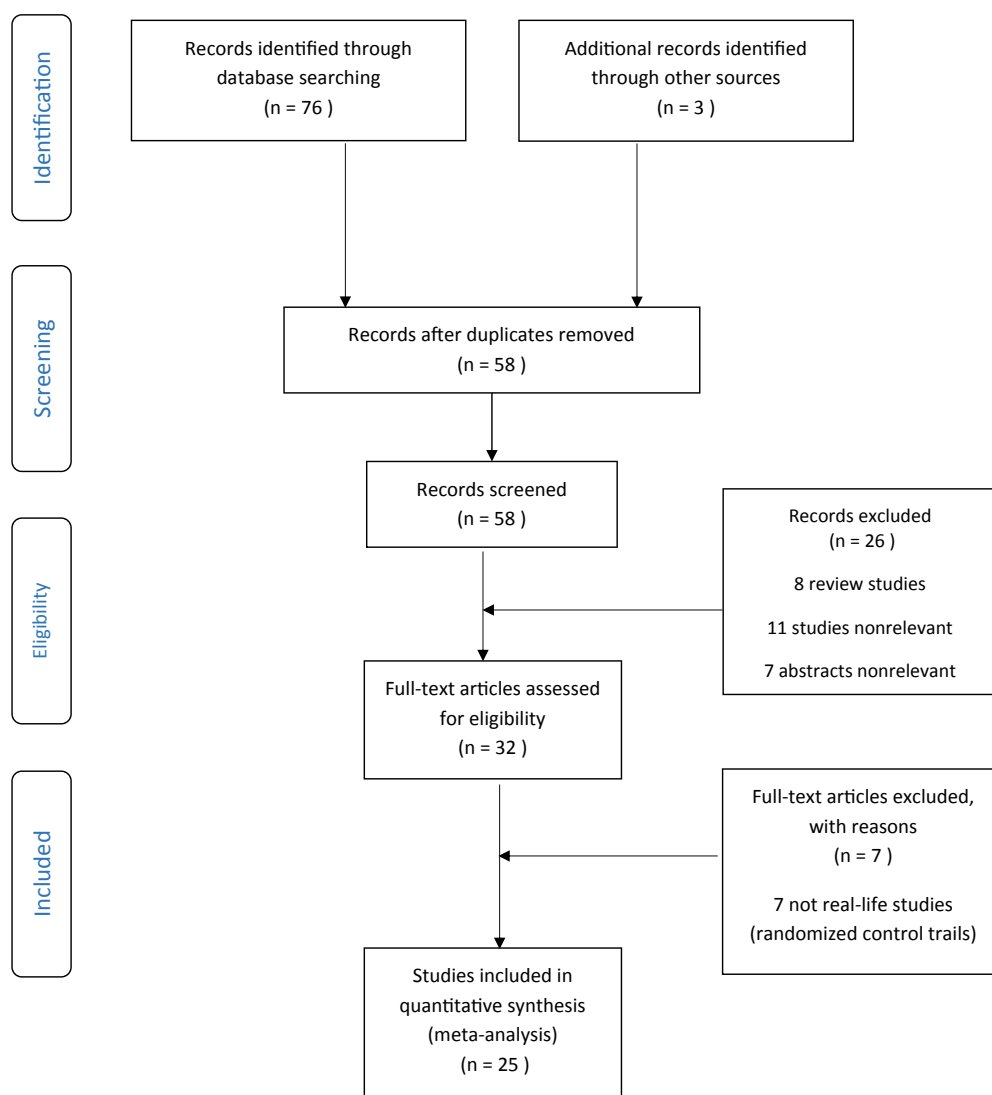


FIGURE 1. PRISMA flow diagram.

Random-effects meta-analyses were performed to quantify pooled effectiveness estimates, taking into account both the dispersion observed within each study (eg, standard error) and the variation in effect sizes across studies (ie, τ^2). Studies were weighted by the inverse of within-study variance plus the between-study variance as calculated by the DerSimonian and Laird method.⁴⁸ Weighted pooled effectiveness estimates and 95% CI were reported. Z-scores (weighted mean divided by the standard error of the weighted mean) and associated *P* values (testing against the null hypothesis of neutral effectiveness) were also provided for each measure to judge the precision of the pooled estimate across studies. Variation in observed effectiveness estimates across studies attributable to heterogeneity was quantified using I^2 , a metric ranging from 0% (indicating that all of the heterogeneity is spurious) to 100% (indicating that all of the heterogeneity is “real” and requires further examination/explanation). Publication and small study bias were assessed graphically and by using Duval and Tweedie’s trim and fill test and Egger’s test,⁴⁹ respectively. Sources of excessive heterogeneity were explored using one-study-removed approaches. All analyses were performed

using Comprehensive Meta-Analysis V3 (Englewood, NJ) and/or StataMP 14 (College Station, Tex).

RESULTS

The flow diagram of study selection is shown in Figure 1. The first search yielded 79 studies, of which 21 studies were excluded because of duplication, 26 studies because of nonrelevant approaches, and 7 studies because they were not “real-life” observational studies. Twenty-five observational studies were included in this meta-analysis. Data on the availability of each outcome at 4-6, 12, and/or 24 months are presented in Table E1 (available in this article’s Online Repository at www.jaci-inpractice.org). Patient demographics and clinical status data are available from one systematic review article.¹⁸ Overall, there was no evidence of publication bias in random-effects meta-analysis results. Therefore, estimates were not altered using trim-and-fill techniques. There was no evidence of excess bias from small study effects.

TABLE I. Summary of meta-analysis statistics

	4-6 mo					12 mo					24 mo				
	Estimate	95% CI	z-score	Q	I ²	Estimate	95% CI	z-score	Q	I ²	Estimate	95% CI	z-score	Q	I ²
GETE good or excellent (%)	77.2%	71.6%-82.8%	27.11	70.3	88.6%	73.0%	65.0%-80.9%	17.99	28.6	89.5%					
Improvement in FEV ₁ (Cohen's <i>d</i>)	0.47	0.36-0.59	8.12	28	64.3%	0.51	0.38-0.64	7.93	21.4	67.3%	0.5	0.24-0.76	3.7	20	85.0%
Improvement in FEV ₁ (% predicted)	9.04%	6.7%-11.4%	7.45	41.1	75.6%	10.6%	8.1%-13.2%	8.11	22	68.2%	9.6%	5.0%-14.2%	4.06	19.8	84.9%
Improvement in total AQLQ (Cohen's <i>d</i>)	1.05	0.70-1.40	5.88	26.5	88.7%	1.2	0.89-1.52	7.44	12.4	88.7%					
Improvement in total AQLQ (score)	1.29	1.01-1.57	7.56	23.4	91.4%	1.51	1.12-1.90	7.56	23.4	91.4%					
Improvement in ACT (Cohen's <i>d</i>)	0.77	0.39-1.15	3.97	66.6	95.5%	1.01	0.50-1.63	3.71	497.5	99.2%	1.22	0.50-1.93	3.35	544.2	99.4%
Improvement in ACT (score)	3.71	1.96-5.45	4.16	97.7	96.9%	4.88	2.44-7.32	3.92	770.1	99.5%	5.6	2.55-8.66	3.6	929.3	99.7%
Proportion of patients requiring OCS (RR)	0.7	0.55-0.84	9.43	5.4*	44.3%	0.46	0.27-0.64	4.75	44.3	90.5%					
Reductions in ICS (Cohen's <i>d</i>)						0.38	0.31-0.46	9.56	3.2*	0.0%					
Reductions in ICS (BE)						264.5	141.62-387.75	4.22	36.8	86.4%					
Reduction in exacerbations (Cohen's <i>d</i>)						0.71	0.57-0.86	9.58	92.2	91.3%					
Reduction in exacerbations (mean)						2.64	2.13-3.16	10.03	103.4	92.3%					
Reduction in hospitalizations (Cohen's <i>d</i>)						0.36	0.21-0.52	4.55	23.7	78.9%	0.48	0.35-0.62	7.06	2.01*	50.3%
Reduction in hospitalizations (mean)						0.53	0.31-0.75	4.73	23.2	78.4%	0.52	0.32-0.71	5.23	3.81*	73.8%

ACT, Asthma Control Test; AQLQ, Juniper Asthma-related Quality-of-Life Measure; BE, beclomethasone equivalents; FEV₁, forced expiratory volume in 1 second; GETE, Global Evaluation of Treatment Effectiveness; ICS, inhaled corticosteroid; OCS, oral corticosteroids; RR, relative risk compared with baseline proportions.

*Nonsignificant between-study heterogeneity.

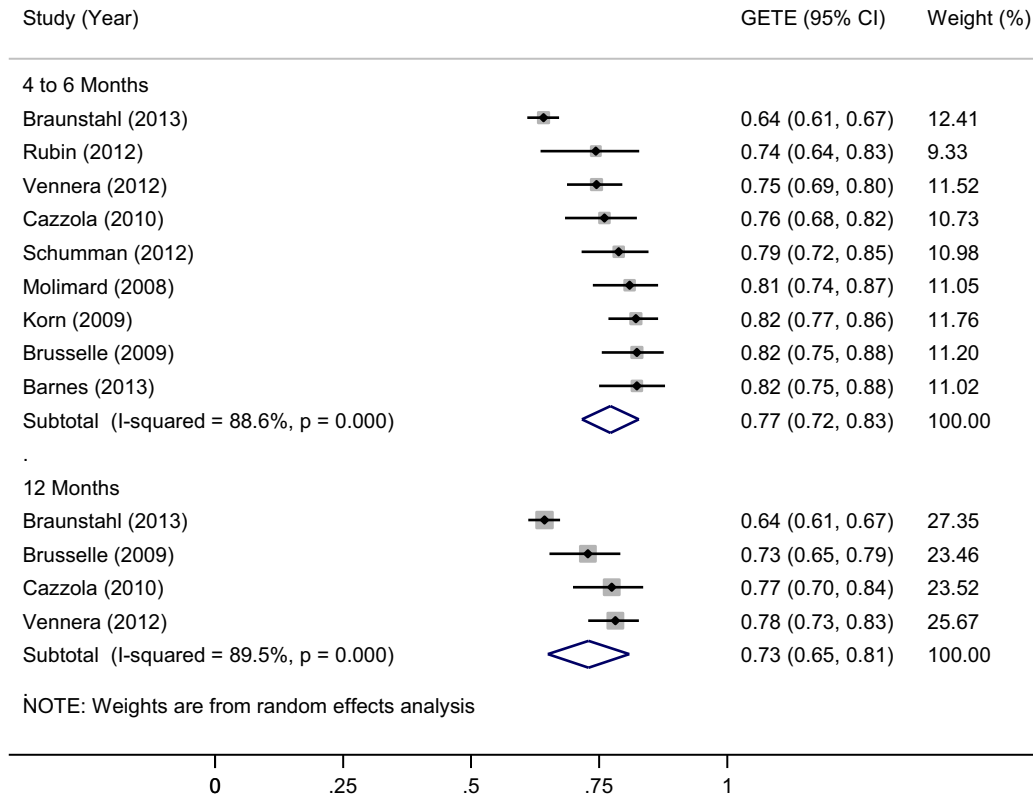


FIGURE 2. Global Evaluation of Treatment Effectiveness. Note: removing Braunstahl et al (2013)³² resulted in more precise estimates and nonsignificant between-study heterogeneity (4-6 months = 79.4% [76.9% to 81.1%], $z = 64.4$, $P < .001$; $Q = 8.3$, $P = .304$, $I^2 = 16.0\%$; 12 months = 76.6% [73.2% to 80.1%], $z = 43.2$, $P < .001$; $Q = 1.6$, $P = .443$, $I^2 = 0.0\%$). CI, Confidence interval; GETE, Global Evaluation of Treatment Effectiveness.

Global evaluation of treatment effectiveness

GETE data were available on 2214 patients after 4-6 months of therapy and on 1491 patients after 12 months of therapy (Table I). On average, 77.2% of patients achieved a good or excellent GETE rating at 4-6 months and 73.0% achieved such GETE rating at 12 months of omalizumab treatment (Figure 2). Removing Braunstahl et al (2013)³² resulted in more precise estimates and nonsignificant between-study heterogeneity (4-6 months = 79.4%, $I^2 = 16.0\%$; 12 months = 76.6%, $I^2 = 0.0\%$).

Forced expiratory volume in 1 second

Data on FEV₁ were available on 1225 patients after 4-6, 1542 patients after 12, and 547 patients after 24 months of therapy (Table I). Compared with baseline values, there were significant improvements in FEV₁ after 4-6 (Cohen's $d = 0.47$; 9.04% predicted FEV₁), 12 (Cohen's $d = 0.51$; 10.6% predicted FEV₁), and 24 months (Cohen's $d = 0.50$; 9.6% predicted FEV₁) of treatment with omalizumab (Figure 3).

Asthma-related quality of life

Data on AQLQ scores before and at 4-6 and at 12 months after omalizumab treatment were available on 547 patients and 1114 patients, respectively (Table I). There were significant and large improvements in asthma-related quality of life after

4-6 (Cohen's $d = 1.05$; 1.29 AQLQ points) and 12 months of therapy (Cohen's $d = 1.20$; 1.51 AQLQ points) (Figure 4, A).

Asthma control

Data on ACT scores in response to omalizumab were available on 5258 patients after 4-6, 6183 patients after 12, and 6123 patients after 24 months of therapy (Table I). There were significant and large improvements in asthma control after 4-6 (Cohen's $d = 0.77$; 3.71 ACT points), 12 (Cohen's $d = 1.01$; 4.88 ACT points), and 24 months of therapy (Cohen's $d = 1.22$; ACT 5.60 points) (Figure 4, B).

Oral and inhaled corticosteroids

Data on OCS requirements before and at 4-6 and 12 months after omalizumab treatment were available on 634 patients and 1394 patients, respectively (Table I). Patients were much less likely to require OCS after 4-6 (RR = 0.70) and 12 months of omalizumab therapy (RR = 0.46, Figure 5, A). Data on ICS requirements before and after 12 months of omalizumab treatment were available on 667 patients (Table I). Significant and small-to-moderate reductions in ICS were noted (Cohen's $d = 0.38$; beclomethasone equivalents = 264.5) (Figure 5, B).

Asthma exacerbations

Data on asthma exacerbations the 12 months before and 12 months after treatment with omalizumab were available on 6650 patients (Table I). Compared with the year before treatment,

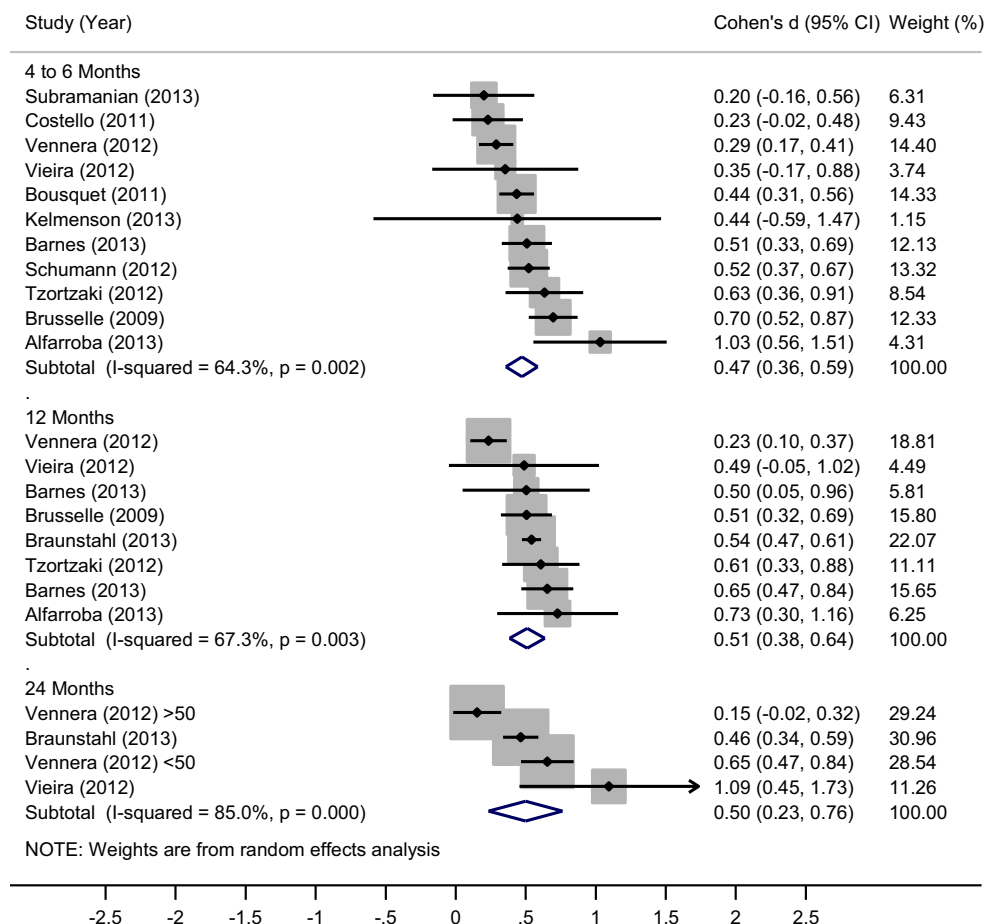


FIGURE 3. Improvements in forced expiratory volume (% predicted). Note: corresponding improvements in FEV₁ (% predicted) were 9.04%, 10.6%, and 9.6% at 4-6 months, 12 months, and 24 months, respectively, after treatment with omalizumab. CI, Confidence interval; FEV₁, forced expiratory volume in 1 s.

there was a significant and large reduction in the number of exacerbations after 12 months (Cohen's $d = 0.71$; 2.64 fewer exacerbations, Figure 6, A).

Asthma-related hospitalizations

Data on asthma hospitalizations the 12 months before and 12 months after treatment with omalizumab were available on 1454 patients (Table I). Compared with the year before treatment, there was a significant but small reduction in the number of hospitalizations after 12 (Cohen's $d = 0.36$; 0.53 fewer hospitalizations, Figure 6, B) and 24 months of therapy with omalizumab (Cohen's $d = 0.48$; 0.52 fewer hospitalizations, Table I).

DISCUSSION

Although randomized controlled trials evaluate the pharmacological efficacy of a drug candidate under constrained conditions, noncontrolled postapproval studies assess the pharmacotherapeutic effectiveness of drugs under "real-life" conditions marked by significant heterogeneity in patients, clinicians, sites, and treatment patterns. The pharmacological efficacy of omalizumab has been reviewed extensively.¹²⁻¹⁷ Our meta-analysis of 25 "real-life" noncontrolled studies documents the effectiveness of omalizumab in the management of adults and

adolescents with severe asthma—most of whom can be assumed to fall in the recently proposed category of severe refractory asthma.⁷ To summarize, the principal findings are that, consistently across the time points for which data were available, omalizumab is associated with improvements in physician-reported GETE, respiratory function (FEV₁), quality of life (AQLQ), asthma control (ACT), and reductions in ICS use, exacerbations, and hospitalizations.

Our meta-analysis covered outcomes measured up to 24 months and, with the exception of GETE, evaluated both changes in the nominal metric and as a standardized effect size in the metric of Cohen's d . By convention, this metric considers a d of approximately 0.2 to be a small effect, a d of approximately 0.5 a medium, and a d of approximately 0.8 and higher a large effect. At 4-6 months, a decision point as to whether to proceed with omalizumab treatment, three-quarters of patients had a good or excellent GETE rating; omalizumab therapy was associated with a medium-sized improvement in FEV₁ and a large improvement in quality of life and asthma symptom control; though the majority of patients still required OCS at that time. By 12 months, about the same proportion of patients still had a good or excellent GETE rating; omalizumab was associated with a medium increase in FEV₁ and, compared with the 4- to

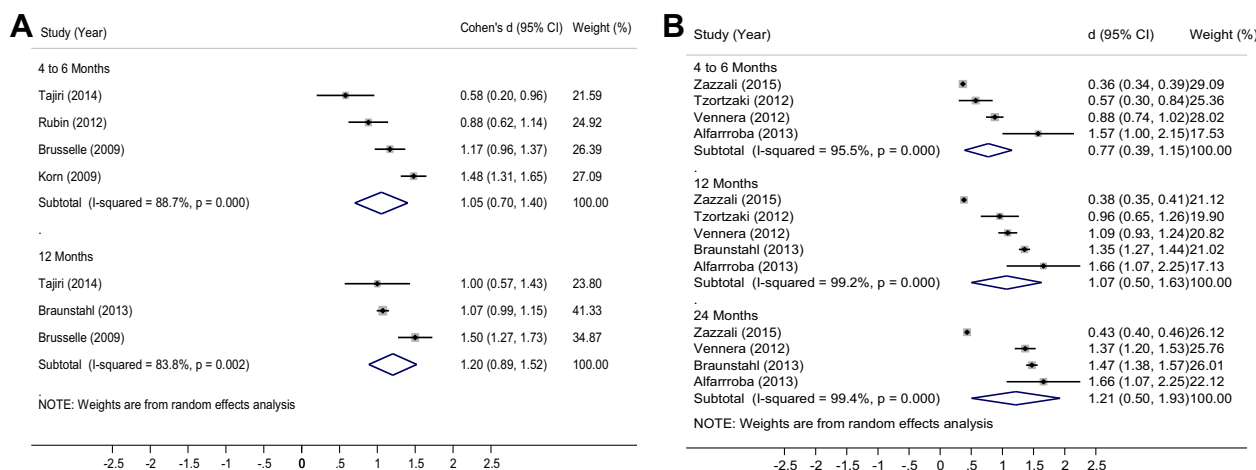


FIGURE 4. A, Improvements in Asthma-related Quality of Life. Note: the observed improvement in Cohen's *d* corresponds with a mean of 1.29 points higher on the AQLQ after 4-6 months and a mean of 1.51 points higher on the AQLQ after 12 months of therapy compared with the year before treatment. **B**, Improvements in asthma control. Note: corresponding improvements in Asthma Control Test scores were 3.71, 4.88, and 5.60 at 4-6 months, 12 months, and 24 months, respectively, after treatment with omalizumab. AQLQ, Asthma-related Quality of Life Questionnaire; CI, confidence interval.

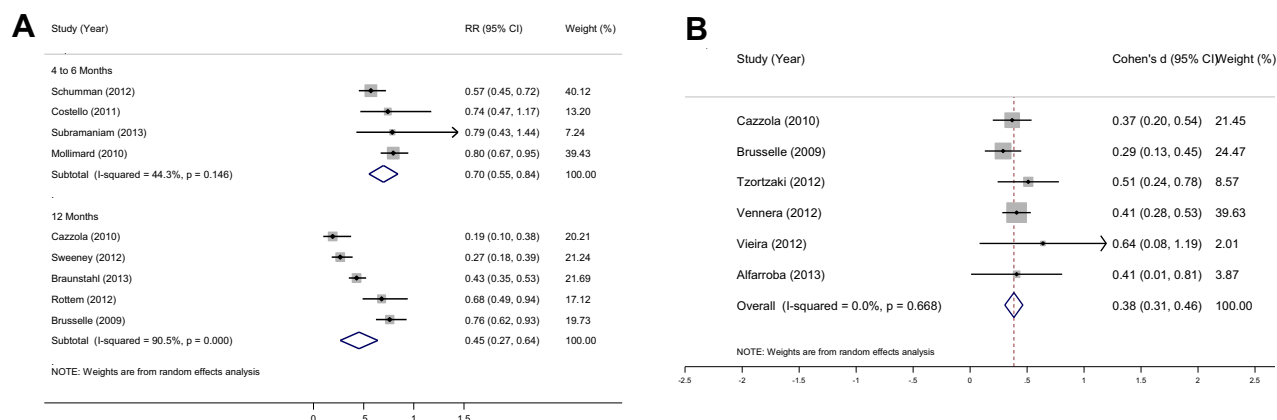


FIGURE 5. A, Reduction in proportion of patients requiring oral corticosteroids (OCS). **B**, Reduction in proportion of patients requiring inhaled corticosteroids (ICS). Note: the observed improvement in Cohen's *d* corresponds with a mean reduction of 264.5 in beclomethasone equivalents after 12 months of therapy compared with the year before treatment. CI, Confidence interval; RR, relative risk compared with baseline proportions.

6-month time point, an even larger improvement in quality of life and symptom control, whereas only about half of patients required OCS support. A small-to-medium reduction in ICS use was observed as well. Per available data, at 24 months, omalizumab was associated with effects on FEV₁ and asthma symptom control similar in size to those observed at 12 months, suggesting a stabilization in asthma status.

Reductions in exacerbations and hospitalizations in association with omalizumab therapy showed similar patterns. These are best reviewed in terms of changes in means and effect sizes. Relative to the year before starting omalizumab, the first 12 months of therapy were associated with reductions of, on average, 2.64 exacerbations (medium-to-large effect) and 0.53 hospitalizations (low-to-medium effect). By 24 months, the average number of hospitalizations was 0.52 (medium effect), indicating a stabilization in hospitalization over 2 years.

Of note, this meta-analysis provides greater support for improvement in subjective outcomes than it does for objective outcomes—with FEV₁ being the exception. This may be a function of the design of many of the studies included in the meta-analysis. Because these were effectiveness and not efficacy studies, more patient-reported outcomes were included than what is typically seen in trials. This has the advantage of being able to capture various aspects of patients' experience in the management of their severe asthma, especially as it relates to improvements over prior treatments.

Our meta-analysis has limitations. In line with the heterogeneity that characterizes observational studies, the *I*² statistics were large, indicating that studies varied in terms of the outcomes observed. Although we attempted to manage this statistically, it does indicate that the generalizability of individual studies is limited. The studies included in our meta-analysis also differed in

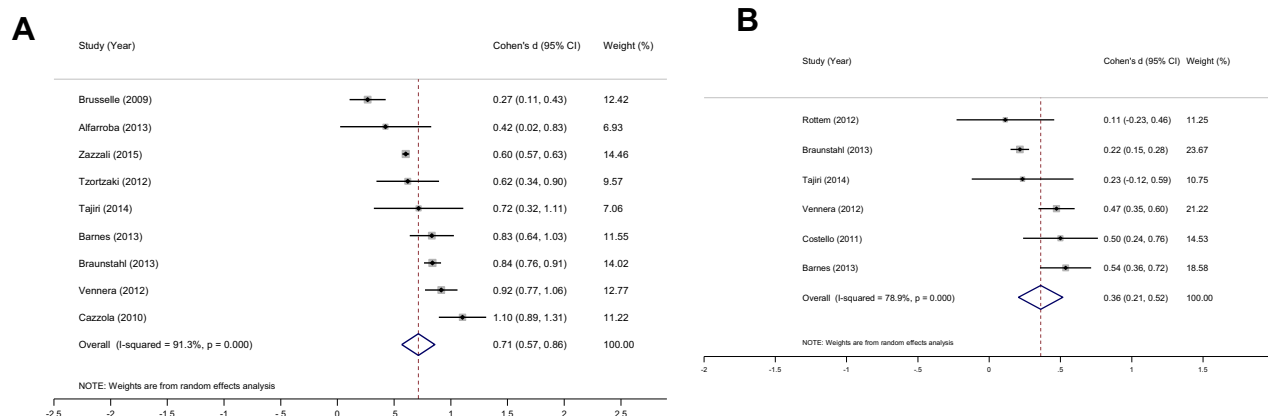


FIGURE 6. A, Reductions in asthma exacerbations. Note: the observed reduction in Cohen's *d* corresponds with a mean of 2.64 fewer exacerbations in the year after omalizumab therapy compared with the year before treatment. **B, Reductions in asthma hospitalizations.** Note: the observed reduction in Cohen's *d* corresponds with a mean of 0.53 fewer hospitalizations in the year after omalizumab therapy compared with the year before treatment. *CI*, Confidence interval.

terms of methodological rigor and, all of them being observational, likely subjected to selection bias in the patients included. Furthermore, these studies were unlikely to be monitored to the extent that clinical trials are; hence the relative accuracy of outcomes reported cannot be assured. Because of the more general fact, we report on a meta-analysis of observational studies, and that we are confined by the methodologies of the studies included, the definition of exacerbation, days of systemic corticosteroid treatment during exacerbations, and the absolute change in FEV₁ in mL were not provided in the included studies. The relative heterogeneity in patient outcomes suggests that there may be patients who respond better to omalizumab. A meta-analysis like ours, which uses aggregate study-level data, cannot answer such subgroup analyses, as this requires access to patient-level data.

However, the observed heterogeneity does not impair our principal findings that in the "real-life setting" add-on therapy with omalizumab is associated with significant improvements in subjective and objective outcomes. What the heterogeneity suggests is that these improvements may show some variation from one country to another, from one health care delivery and health care financing system to another, and from one clinical setting to another. Furthermore, heterogeneity is more important in the meta-analysis of randomized controlled trials because the emphasis is on studies confirming one another. In contrast, in observational studies like the ones included in our meta-analysis, the focus is on understanding how omalizumab works in the real world, without the controls and constraints inherent to randomized controlled trials.

In conclusion, our meta-analysis provides, to the best of our knowledge, the first quantitative synthesis evidence that the effectiveness of omalizumab therapy under heterogeneous, noncontrolled conditions mirrors, complements, and extends the efficacy shown in randomized controlled trials in the management of severe allergic asthma in adults.

REFERENCES

- Martinez FD, Vercelli D. Asthma. *Lancet* 2013;382:1360-72.
- O'Byrne PM, Pedersen S, Schatz M, Thoren A, Ekholm E, Carlsson LG, et al. The poorly explored impact of uncontrolled asthma. *Chest* 2013;143:511-23.
- Braman S. The global burden of asthma. *Chest* 2006;130:4S-12.
- Bateman E, Hurd S, Barnes P, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31:143-78.
- Cazzoletti L, Marco A, Janson C, Corsico A, Jarvis D, Pin I, et al. Asthma control in Europe: a real-world evaluation based on an international population-based study. *J Allergy Clin Immunol* 2007;120:1360-7.
- de Marco R, Cazzoletti L, Cerveri I, Corsico A, Bugiani M, Accordini S, et al. Are the asthma guideline goals achieved in daily practice? A population-based study on treatment adequacy and the control of asthma. *Int Arch Allergy Immunol* 2005;138:225-34.
- Bel EH, Sousa A, Fleming L, Bush A, Chung KF, Versnel J, et al. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicines Initiative (IMI). *Thorax* 2011;66:910-7.
- Hekking PW, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. *J Allergy Clin Immunol* 2015;135:896-902.
- Gould H, Sutton B, Beavil A, Beavil RL, McCloskey N, Coker HA, et al. The biology of IgE and the basis of allergic disease. *Ann Rev Immunol* 2003;21:579-628.
- Solèr M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001;18:254-61.
- Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. *Chest* 2004;125:1378-86.
- D'Amato G, Perticone M, Bucchioni E, Salzillo A, D'Amato M, Liccardi G. Treating moderate-to-severe allergic asthma with anti-IgE monoclonal antibody (omalizumab). An update. *Eur Ann Allergy Clin Immunol* 2010;42:135-40.
- Humbert M, Beasley R, Ayres J, Slavin R, Hébert J, Bousquet 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.
- Buhl R, Hanf G, Solèr M, Bensch G, Wolfe J, Everhard F, et al. The anti-IgE antibody omalizumab improves asthma-related quality of life in patients with allergic asthma. *Eur Respir J* 2002;20:1088-94.
- Holgate S, Buhl R, Bousquet J, Smith N, Panahloo Z, Jimenez P. The use of omalizumab in the treatment of severe allergic asthma: a clinical experience update. *Resp Med* 2009;103:1098-113.
- Kuhl K, Hanania N. Targeting IgE in asthma. *Curr Opin Pulm Med* 2012;18:1-5.
- Pelaia G, Gallelli L, Renda T, Romeo P, Busceti MT, Grembiale RD, et al. Update on optimal use of omalizumab in management of asthma. *J Asthma Allergy* 2011;4:49-59.
- Abraham I, Alhossan A, Lee CS, Kutbi H, MacDonald K. "Real-life" effectiveness studies of omalizumab in adult patients with severe allergic asthma: systematic review. *Allergy* 2016;71:593-610.
- Molimard M, de Blay F, Didier A, Le Gros V. Effectiveness of omalizumab (xolair) in the first patients treated in real-life practice in France. *Respir Med* 2008;102:71-6.

20. Korn S, Thielen A, Seyfried S, Taube C, Kornmann O, Buhl R. Omalizumab in patients with severe persistent allergic asthma in a real-life setting in Germany. *Respir Med* 2009;103:1725-31.
21. Brusselle G, Michils A, Louis R, Dupont L, Van de Maele B, Delobbe A, et al. "Real-life" effectiveness of omalizumab in patients with severe persistent allergic asthma: the persist study. *Respir Med* 2009;103:1633-42.
22. Molimard M, Buhl R, Niven R, Le Gros V, Thielen A, Thirlwell J, et al. Omalizumab reduces oral corticosteroid use in patients with severe allergic asthma: real-life data. *Respir Med* 2010;104:1381-5.
23. Cazzola M, Camiciottoli G, Bonavia M, Gulotta C, Ravazzi A, Alessandrini A, et al. Italian real-life experience of omalizumab. *Respir Med* 2010;104:1410-6.
24. Costello RW, Long DA, Gaine S, Mc Donnell T, Gilmartin JJ, Lane SJ. Therapy with omalizumab for patients with severe allergic asthma improves asthma control and reduces overall healthcare costs. *Ir J Med Sci* 2011;180: 637-41.
25. Rottem M. Omalizumab reduces corticosteroid use in patients with severe allergic asthma: real-life experience in Israel. *J Asthma* 2012;49:78-82.
26. Tzortzaki EG, Georgiou A, Kampas D, Lemessios M, Markatos M, Adamidi T, et al. Long-term omalizumab treatment in severe allergic asthma: the south-eastern Mediterranean "real-life" experience. *Pulm Pharmacol Ther* 2012;25: 77-82.
27. Vennema Mdel C, Pérez de Llano L, Bardagí S, Ausin P, Sanjuas C, González H, et al. Omalizumab therapy in severe asthma: experience from the Spanish registry— some new approaches. *J Asthma* 2012;49:416-22.
28. Sweeney J, Brightling CE, Menzies-Gow A, Niven R, Patterson CC, Heaney LG. Clinical management and outcome of refractory asthma in the UK from the British thoracic society difficult asthma registry. *Thorax* 2012;67:754-6.
29. Schumann C, Kropf C, Wibmer T, Rüdiger S, Stoiber KM, Thielen A, et al. Omalizumab in patients with severe asthma: the XCLUSIVE study. *Clin Respir J* 2012;6:215-27.
30. Grimaldi-Bensouda L, Zureik M, Aubier M, Humbert M, Levy J, Benichou J, et al. Does omalizumab make a difference to the real-life treatment of asthma exacerbations? Results from a large cohort of patients with severe uncontrolled asthma. *Chest* 2013;143:398-405.
31. Barnes N, Menzies-Gow A, Mansur AH, Spencer D, Percival F, Radwan A, et al. Effectiveness of omalizumab in severe allergic asthma: a retrospective UK real-world study. *J Asthma* 2013;50:529-36.
32. Braunstahl G, Chlumský J, Peachey G, Chen CW. Reduction in oral corticosteroid use in patients receiving omalizumab for allergic asthma in the real-world setting. *Allergy Asthma Clin Immunol* 2013;9:47.
33. Korn S, Schumann C, Kropf C, Stoiber K, Thielen A, Taube C, et al. Effectiveness of omalizumab in patients 50 years and older with severe persistent allergic asthma. *Ann Allergy Asthma Immunol* 2010;105:313-9.
34. Bousquet J, Siergiejko Z, Swiebocka E, Humbert M, Rabe KF, Smith N, et al. Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma. *Allergy* 2011;66:671-8.
35. Rubin S, Souza-Machado A, Andradre-Lima M, Ferreira F, Honda A, Matozo TM. Effect of omalizumab as add-on therapy on asthma-related quality of life in severe allergic asthma: a Brazilian study (QUALITX). *J Asthma* 2012; 49:288-93.
36. Vieira T, Oliveira J, Castel-Branco M. Short and long-term quality of life and asthma control with omalizumab therapy in a real life setting in Portugal. *Allergol Immunopathol (Madr)* 2014;42:3-10.
37. Alfaro S, Videira W, Galvão-Lucas C, Carvalho F, Barbara C. Clinical experience with omalizumab in a Portuguese severe asthma unit. *Rev Port Pneumol* 2014;20:78-83.
38. Kelmenson DA, Kelly VJ, Winkler T, Kone MT, Musch G, Melo MFV, et al. The effect of omalizumab on ventilation and perfusion in adults with allergic asthma. *Am J Nucl Med Mol Imaging* 2013;3:350-60.
39. Subramaniam A, Al-Alawi M, Hamad S, O'Callaghan J, Lane SJ. A study into efficacy of omalizumab therapy in patients with severe persistent allergic asthma at a tertiary referral center for asthma in Ireland. *QJM* 2013;106: 631-4.
40. Tiro J, Contreras E, Pozo M, Vera J, Linnemann D. Real life study of three years omalizumab in patients with difficult-to-control asthma. *Allergol Immunopathol (Madr)* 2015;43:120-6.
41. Novelli F, Latorre M, Vergura L, Caiaffa MF, Camiciottoli G, Guarnieri G, et al. Asthma control in severe asthmatics under treatment with omalizumab: a cross-sectional observational study in Italy. *Pulm Pharmacol Ther* 2015;31: 123-9.
42. Tajiri T, Niimi A, Matsumoto H, Ito I, Oguma T, Otsuka K, et al. Comprehensive efficacy of omalizumab for severe refractory asthma: a time-series observational study. *Ann Allergy Asthma Immunol* 2014;113:470-5.
43. Zazzali JL, Raimundo KP, Trzaskoma B, Rosén KE, Schatz M. Changes in asthma control, work productivity, and impairment with omalizumab: 5-year EXCELS study results. *Allergy Asthma Proc* 2015;36:283-92.
44. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992;47:76-83.
45. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113:59-65.
46. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA* 2000;283:2008-12.
47. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
48. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
49. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.

ONLINE REPOSITORY

TABLE E1. Indices of omalizumab effectiveness

Study	Evaluable N at baseline (omalizumab-treated)	GETE	FEV ₁	ACT	AQLQ	OCS	Exacerbations	Hospitalizations
4-6 mo								
Molimard et al, 2008 ¹⁹	146	✓						
Brusselle et al, 2009 ²¹	158	✓	✓		✓			
Korn et al, 2009 ²⁰	280	✓			✓			
Cazzola et al, 2010 ²³	142	✓						
Korn et al, 2010 ³³	471							
Molimard et al, 2010 ²²	166					✓		
Bousquet et al, 2011 ³⁴	272		✓					
Costello et al, 2011 ²⁴	63		✓			✓		
Rottem, 2012 ²⁵	33							
Rubin et al, 2012 ³⁵	78	✓						
Schumann et al, 2012 ²⁹	195	✓	✓		✓	✓		
Sweeney et al, 2012 ²⁸	59							
Tzortzaki et al, 2012 ²⁶	60		✓	✓				
Vennera et al, 2012 ²⁷	266	✓	✓	✓				
Vieira et al, 2014 ³⁶	15		✓					
Alfarroba et al, 2014 ³⁷	26		✓	✓				
Barnes et al, 2013 ³¹	136	✓	✓					
Braunstahl et al, 2013 ³²	925	✓						
Grimaldi-Bensouda et al, 2013 ³⁰	374							
Kelmenson et al, 2013 ³⁸	4		✓		✓			
Subramaniam et al, 2013 ³⁹	30		✓			✓		
Tiro et al, 2015 ⁴⁰	47							
Novelli et al, 2015 ⁴¹	306							
Tajiri et al, 2014 ⁴²	31							
Zazzali et al, 2015 ⁴³	576			✓	✓			
Evaluable n		2214	1225	5258	547	634	—	—
12 mo								
Molimard et al, 2008 ¹⁹	146							
Brusselle et al, 2009 ²¹	158	✓	✓		✓	✓	✓	
Korn et al, 2009 ²⁰	280							
Cazzola et al, 2010 ²³	142	✓				✓	✓	
Korn et al, 2010 ³³	471							
Molimard et al, 2010 ²²	166							
Bousquet et al, 2011 ³⁴	272							
Costello et al, 2011 ²⁴	63							✓
Rottem, 2012 ²⁵	33					✓		✓
Rubin et al, 2012 ³⁵	78							
Schumann et al, 2012 ²⁹	195							
Sweeney et al, 2012 ²⁸	59					✓		
Tzortzaki et al, 2012 ²⁶	60		✓	✓			✓	
Vennera et al, 2012 ²⁷	266	✓	✓	✓			✓	✓
Vieira et al, 2014 ³⁶	15		✓					
Alfarroba et al, 2014 ³⁷	26		✓	✓			✓	
Barnes et al, 2013 ³¹	136		✓				✓	✓
Braunstahl et al, 2013 ³²	925	✓	✓	✓		✓	✓	✓
Grimaldi-Bensouda et al, 2013 ³⁰	374							
Kelmenson et al, 2013 ³⁸	4							
Subramaniam et al, 2013 ³⁹	30							
Tiro et al, 2015 ⁴⁰	47							
Novelli et al, 2015 ⁴¹	306							
Tajiri et al, 2014 ⁴²	31						✓	✓

(continued)

TABLE E1. (Continued)

Study	Evaluable N at baseline (omalizumab-treated)	GETE	FEV ₁	ACT	AQLQ	OCS	Exacerbations	Hospitalizations
Zazzali et al, 2015 ⁴³	576			✓	✓		✓	
Evaluable n		1491	1542	6183	1114	1394	6650	1454
24 mo								
Molimard et al, 2008 ¹⁹	146							
Brusselle et al, 2009 ²¹	158							
Korn et al, 2009 ²⁰	280							
Cazzola et al, 2010 ²³	142							
Korn et al, 2010 ³³	471							
Molimard et al, 2010 ²²	166							
Bousquet et al, 2011 ³⁴	272							
Costello et al, 2011 ²⁴	63							
Rottem, 2012 ²⁵	33							
Rubin et al, 2012 ³⁵	78							
Schumann et al, 2012 ²⁹	195							
Sweeney et al, 2012 ²⁸	59							
Tzortzaki et al, 2012 ²⁶	60							
Vennera et al, 2012 ²⁷	266		✓	✓			✓	✓
Vieira et al, 2014 ³⁶	15		✓					
Alfarroba et al, 2014 ³⁷	26			✓			✓	
Barnes et al, 2013 ³¹	136							
Braunstahl et al, 2013 ³²	925		✓	✓			✓	✓
Grimaldi-Bensouda et al, 2013 ³⁰	374							
Kelmenson et al, 2013 ³⁸	4							
Subramaniam et al, 2013 ³⁹	30							
Tiro et al, 2015 ⁴⁰	47							
Novelli et al, 2015 ⁴¹	306							
Tajiri et al, 2014 ⁴²	31							
Zazzali et al, 2015 ⁴³	576			✓				
Evaluable n		—	547	6123	—	—	1217	1191

ACT, Asthma Control Test; AQLQ, Asthma-related Quality-of-Life Questionnaire; FEV₁, forced expiratory volume in 1 second; GETE, Global Evaluation of Treatment Effectiveness; OCS, oral corticosteroids.