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To cite this article: Kenneth M. Faulkner, Karen MacDonald, Ivo Abraham, Abdulaziz Alhossan & Christopher S. Lee (2021) 'Real-world' effectiveness of omalizumab in adults with severe allergic asthma: a meta-analysis, *Expert Review of Clinical Immunology*, 17:1, 73-83, DOI: 10.1080/1744666X.2020.1856658

To link to this article: <https://doi.org/10.1080/1744666X.2020.1856658>



Published online: 14 Dec 2020.



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ORIGINAL RESEARCH



'Real-world' effectiveness of omalizumab in adults with severe allergic asthma: a meta-analysis

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ABSTRACT

Background: Severe asthma affects 5–10% of the 350 million people with asthma worldwide. Findings from the authors' previous meta-analysis supported omalizumab use as an adjuvant treatment for severe allergic asthma. The publication of fourteen new articles necessitates an update of the meta-analysis.

Objective: To evaluate the 'real-world' effectiveness of omalizumab in the treatment of acute allergic asthma in adults by calculating pooled effects estimates from data in published articles.

Methods: Articles on omalizumab effectiveness in 'real-world' settings were identified. Effect sizes, including point estimates of the proportion of patients who met a given criteria, mean improvements relative to baseline, and change in the proportion of patients requiring oral corticosteroids compared to baseline were extracted. Meta-analysis of proportions was conducted to pool effect sizes based on proportions. Standardized mean differences (Hedges' *g*) were calculated from means and standard deviations. Relative risk was calculated from changes in proportions. Variability within and between studies was evaluated.

Results: Omalizumab increases the percentage of individuals rated 'good' or 'excellent' on the Global Evaluation of Treatment Effectiveness Scale. Omalizumab also improves respiratory function, quality-of-life, and asthma control while reducing medication usage, exacerbations, hospitalizations, and adverse events.

Conclusion: 'Real-world' evidence continues to support the use of omalizumab as adjuvant treatment for severe allergic asthma.

ARTICLE HISTORY

Received 6 August 2020
Accepted 24 November 2020

KEYWORDS

Omalizumab; effectiveness; asthma; adults; meta-analysis

1. Introduction

Asthma is a chronic respiratory condition that affects over 350 million people globally [1]. Approximately 5–10% of those with asthma have severe asthma, which is characterized by persistent symptoms despite treatment with oral corticosteroids or a combination of long-acting beta-agonists and inhaled glucocorticoids [2]. Poor symptom control is associated with a high risk of mortality and worse quality of life for individuals with asthma, so additional therapies are necessary to improve symptoms and asthma-associated quality of life [1,3,4].

Omalizumab is a monoclonal antibody that targets IgE and is associated with improvement in asthma symptoms and quality of life in clinical trials [5–7]. Improvements in lung function, asthma control, quality of life, medication use, exacerbations, and asthma-related hospitalizations also were shown in a meta-analysis of observational studies of omalizumab [8]. Several additional articles have been published since the last meta-analysis, necessitating the need for an update. The purpose of this paper is to quantitatively synthesize the findings from all published articles on the real-world

effectiveness of omalizumab in order to provide guidance on what level of results could be anticipated in clinical practice.

2. Methods

2.1. Search strategy

Three electronic databases (PubMed, Embase, and Cochrane Library) were searched for relevant research using the keywords 'IgE,' 'immunoglobulin E,' 'omalizumab,' 'asthma,' 'effectiveness,' 'real-life,' and 'real world.' No restrictions on the date, sample size, or language were imposed on the search. Abstracts without accompanying articles were not included due to limitations on the data available for extraction. Reference lists from identified articles also were reviewed for relevant articles and the literature was monitored for new publications on the subject. The search yielded articles included in the previous meta-analysis [8] and several new articles published since the previous meta-analysis in 2017. A systematic review including data from recent articles had been published previously [9]; the current work represents the

formal quantitative synthesis of all known articles on the real-world effectiveness of omalizumab globally.

2.2. Outcome measures

This meta-analysis focuses on common outcomes reported across multiple articles. The Global Evaluation of Treatment Effectiveness (GETE) was used to determine the effectiveness of omalizumab in several articles. In the GETE, physicians are asked to rate the overall response to a given treatment on a 5-point scale (excellent, good, moderate, poor, or worsening) [10]. A GETE rating of good or excellent indicated that the treatment was effective. Forced expiratory volume in one second (FEV₁) also was frequently used to determine treatment effectiveness. In this meta-analysis, change in FEV₁ % of expected is evaluated over each time interval. Several articles included the Asthma Control Test (ACT) as a measure of effectiveness. Each of the five items on the ACT addresses an aspect of asthma control, from the frequency of medication use to how asthma interferes with normal activity [11]. Higher scores indicate better asthma control [11,12]. The Asthma-related Quality of Life Questionnaire (AQLQ) was used as an indicator of treatment effectiveness in several articles. The AQLQ is a 32-item questionnaire that encompasses four domains: activity limitations, symptoms, emotional function, and exposure to environmental stimuli [13]. Participants are asked to rate the influence asthma has on each item on a 7-point scale [13]. Higher scores indicate fewer limitations or less distress due to asthma [13]. An improvement of ≥ 0.5 on the 7-point scale is indicative of clinically significant improvement on the AQLQ [14]. Change in the proportion of participants requiring oral corticosteroids (OCS) and a reduction in the mean dose of inhaled corticosteroids (ICS) in beclomethasone equivalents was reported as an indication of treatment effectiveness in several articles. The mean number of exacerbations per year and the mean number of hospitalizations also were reported to indicate the effectiveness of omalizumab. The proportion of patients who experienced an adverse event (any degree of severity) while enrolled in the study also was included in this analysis. As GETE and FEV₁ are clinical indicators, these are considered 'primary' outcomes in this analysis. All other measures are considered 'secondary' outcomes.

2.3. Critical appraisal of retrieved studies

All retrieved articles were appraised using the Real Life Evidence Assessment Tool (RELEVANT) to determine the strength of existing evidence [15,16]. These guidelines consist of 11 primary criteria and 10 secondary criteria from 7 quality domains [15,16]. The presence or absence of each criterion is noted. The absence of a primary criterion is considered a 'fatal flaw' by RELEVANT guidelines [15,16].

2.4. Data extraction

Published guidelines for the conduct and reporting of meta-analyses of observational studies directed this analysis [17]. Data from retrieved articles were extracted, verified by

a second researcher, and entered into a spreadsheet for ease of analysis. Disagreements on extracted data were resolved by the two reviewers or by the inclusion of a third reviewer to help the reviewers reach a consensus.

Three types of effect sizes were extracted from the included articles. First, point estimates of the proportion of patients meeting a specific criterion, such as the proportion of patients rated as good or excellent on the GETE scale, were calculated at each time point based on the number of patients achieving the criterion compared to the total sample. Second, mean improvements relative to the score at enrollment, such as improvements in FEV₁ or reduction in the mean dose of ICS, were extracted as mean score and standard deviation pre-treatment and post-treatment. Third, the number of participants using OCS at each time point compared to the number of participants using OCS prior to starting therapy with omalizumab were extracted and are presented as relative risk (RR).

2.5. Statistical analysis

Standardized mean differences in the form of Hedges' g were calculated from the extracted means and standard deviations, as several of the included studies had small samples [18]. Small effect sizes were defined as Hedges' g of 0.2, medium effect sizes were defined as Hedges' g of 0.5, and large effect sizes were defined as Hedges' g of ≥ 0.8 [19]. The proportion of participants who had an adverse event during the study period or who had a GETE score of good or excellent was calculated for those two variables.

Random effect meta-analyses were conducted to quantify the pooled effect of omalizumab on continuous outcomes. Random effect meta-analysis of proportions was performed using the metaprop command in Stata to quantify pooled GETE scores and the proportion of patients who experienced an adverse event [20]. An assumption of random effect meta-analysis is that effect sizes are not constant, and that observed variability in the effect sizes is due to a combination of sampling error and differences in the effect sizes among the samples [21]. The observed variability in effect size within each study (measured by standard error) and variability between studies (measured by τ^2) are factored into the calculation of pooled effect estimates. Effect sizes from individual studies were weighted using the inverse variance method described by DerSimonian and Laird [22]. Weighted pooled estimates and 95% confidence intervals are reported. The precision of pooled estimates is reflected in Z-scores (weighted mean divided by the standard error of the weighted mean) and p -values that reflect the significance against the null hypothesis that omalizumab has no effect on outcomes. The amount of between-study variability attributed to heterogeneity is presented in the metric of Q and I^2 . A statistically significant Q statistic ($p < 0.05$) is indicative of significant between-study heterogeneity. Values for I^2 range from 0% (indicating that all the heterogeneity is spurious) to 100% (indicating that all the heterogeneity is 'real' and requires additional assessment). Funnel plots were generated to evaluate publication bias, and Egger's test was performed to quantify bias from small-samples [23–25]. Unstandardized

weighted mean differences and the associated 95% confidence interval (CI) also are reported to improve interpretability. A sensitivity analysis was performed to determine if effect sizes differed when studies were analyzed by study design (prospective vs. retrospective) using random effect meta-regression. Statistical significance was determined by reviewing coefficients, 95% confidence intervals, and associated *p* values. All analyses were conducted using Stata version 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.)

3. Results

The identification and selection of articles for inclusion in this meta-analysis is outlined in Figure 1. Forty-four articles representing 42 studies on 'real-world' effectiveness of omalizumab remained after exclusion of duplicates, reviews, and irrelevant articles [14,26–68]. Sociodemographic and clinical characteristics of the samples can be found in a recent systematic review [9]. Ten articles were excluded from this meta-analysis due to obscure evaluation time points (e.g. 60.7 ± 30.9 months, 9.2 months) [59–68]. Removal of these articles resulted in

a final sample of 34 articles from 32 studies on omalizumab effectiveness for inclusion in this meta-analysis [14,26–58]. Summary of all meta-analyses is presented in Table 1. Funnel plots and Egger's test for all outcomes were not suggestive of publication bias or small sample effects across analyses. Quality appraisal revealed that all studies were deficient by at least one primary criterion Table 2, suggesting that the evidence was low quality.

3.1. Global evaluation of treatment effectiveness

Data on omalizumab effectiveness based on GETE were available for 6931 participants at 4–6 months and 4181 participants at 1 year post initiation of the medication Figure 2. On average, 77% of the participants at 4–6 months and 76% of the participants at 1 year had a GETE rating of good or excellent. There was significant and considerable heterogeneity in GETE ratings across studies at both time points. Comparison of effect sizes by research design at 4–6 months indicated no significant differences ($p=0.64$). Comparison at 1 year was not possible as all studies that evaluated GETE at 1 year were prospective.

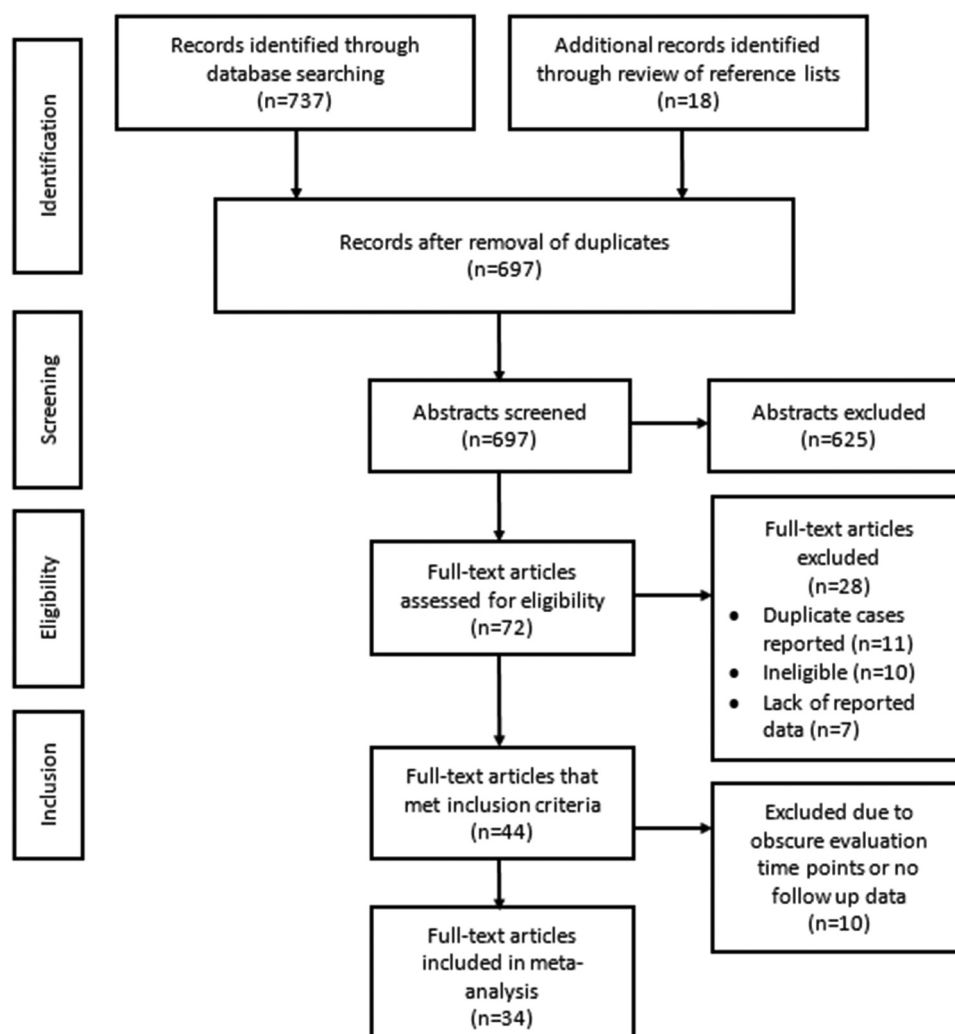


Figure 1. PRISMA diagram.

Table 1. Results of meta-analysis.

Outcome	4–6 months					1 year					2 years				
	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	0.77	[0.71, 0.82]	29.98	289.06*	95.5%	0.76	[0.66, 0.85]	18.10	59.08*	92.2%	-	-	-	-	-
Improvement in FEV ₁	0.44	[0.34, 0.53]	8.85	26.75*	40.2%	0.54	[0.36, 0.72]	5.90	50.90*	78.4%	0.61	[0.30, 0.92]	3.89	27.22*	85.3%
Improvement in AQLQ	1.03	[0.78, 1.29]	8.06	45.01*	80.0%	1.11	[0.82, 1.40]	7.46	10.75*	72.1%	-	-	-	-	-
Improvement in ACT	0.96	[0.73, 1.18]	8.32	27.41*	63.5%	1.20	[1.02, 1.38]	13.16	20.84*	56.8%	1.49	[1.32, 1.66]	17.06	5.73	30.2%
Reduction in proportion on OCS (RR)	0.56	[0.42, 0.75]	3.89	27.61*	74.6%	0.65	[0.44, 0.95]	2.23	88.36*	90.9%	0.49	[0.39, 0.60]	6.68	1.15	0.0%
Reduction in mean dose of ICS	0.32	[0.11, 0.54]	2.97	6.95	42.4%	0.41	[0.29, 0.53]	6.60	1.40	0.0%	0.58	[0.26, 0.90]	3.54	2.67	25.0%
Reduction in exacerbations	-	-	-	-	-	0.84	[0.48, 1.21]	4.51	537.27*	97.8%	1.04	[0.52, 1.56]	3.93	26.43*	92.4%
Reduction in asthma-associated hospitalizations	-	-	-	-	-	0.35	[0.16, 0.54]	3.60	85.12*	90.6%	-	-	-	-	-
Adverse events	-	-	-	-	-	0.20	[0.09, 0.34]	5.14	50.68*	94.1%	0.33	[0.16, 0.53]	5.37	123.24*	97.5%

Note: ACT = asthma control test, AQLQ = asthma quality-of-life questionnaire, FEV₁ = forced expiratory volume in 1 second (percent of predicted), CI = confidence interval, GETE = global evaluation of treatment effectiveness, ICS = inhaled corticosteroids, OCS = oral corticosteroids, RR = relative risk, * indicates $p < 0.05$

Table 2. Critical appraisal of included studies using the RELEVANT tool.

First Author (year)	Clear research question	Defined population	Comparison group defined	Exposure or treatment clearly defined	Primary outcomes defined	Potential confounders addressed	Groups compared at baseline	Results are clearly presented for primary and secondary endpoints	Results consistent with known information or explanation given	Clinical relevance is discussed	Conflicts of interest and funding are reported
Brusselle (2009)	Y	Y	N	Y*	Y	N	N/A	Y	Y	Y	Y
Adachi (2018)	Y	Y	N	Y	Y	Y	N/A	Y	Y	Y	Y
Alfarroba (2014)	Y	N	N	Y*	Y	N	N/A	Y	Y	Y	Y
Ancochea (2014)	Y	Y	N	Y*	Y	N	N/A	Y	Y	N	Y
Barnes (2013)	Y	Y	N	Y*	Y	N	N/A	Y	Y	N	Y
Bousquet (2011)	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y
Braunsthahl (2014)	Y	Y	N	Y*	Y	N	N/A	Y	Y	Y	Y
Braunsthahl (2013)†	Y	Y	N	Y*	Y	N	N/A	Y	Y	Y	Y
Braunsthahl (2013)‡	Y	Y	N	Y*	Y	N	N/A	Y	Y	Y	Y
Cazzola (2010)	Y	Y	N	Y	Y	N	N/A	Y	Y	Y	Y
Costello (2011)	Y	Y	N	Y	Y	N	N/A	Y	Y	Y	Y
Gouder (2015)	Y	Y	N	Y	Y	N	N/A	Y	N	N	Y
Humbert (2018)	Y	Y	N	Y*	Y	N	N/A	Y	Y	N	Y
Kawamatawong (2018)	Y	Y	N	Y*	Y	N	N/A	Y	Y	N	N
Kelmenson (2013)	Y	Y	N	Y*	Y	N	N/A	Y	Y	N	Y
Korn (2009)	Y	Y	N	Y*	Y	N	N/A	Y	Y	Y	Y
Kuprys-Lipinska (2016)	Y	Y	N	Y	Y	N	N/A	Y	Y	Y	Y
Maltby (2017)	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y
Molimard (2008)	Y	N	N	Y	Y	N	N/A	Y	Y	Y	Y
Niven (2016)	Y	Y	N	Y	Y	N	N/A	Y	Y	Y	Y
Nygaard (2017)	Y	Y	H	N	Y	N	N/A	Y	Y	Y	Y
Özgür (2013)	Y	Y	N	Y*	Y	N	N/A	Y	Y	N	Y
Paganin (2017)	Y	Y	N	Y	Y	Y	N/A	Y	Y	N	Y
Rottem (2012)	Y	Y	N	Y*	Y	N	N/A	Y	Y	Y	Y
Rubin (2012)	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Schumann (2012)	Y	Y	N	Y	Y	N	N/A	Y	Y	Y	Y
Subramaniam (2013)	Y	Y	N	Y*	Y	H	N/A	Y	Y	Y	Y
Sweeney (2012)	N	N	N	N	N	N	N/A	Y	N	Y	Y
Tajiri (2014)	Y	Y	N	Y*	Y	N	N/A	Y	Y	Y	Y
Tzortzaki (2012)	Y	Y	N	Y*	Y	N	N/A	Y	Y	Y	Y
Vennera (2012)	Y	Y	N	Y	Y	N	N/A	Y	Y	Y	Y
Viera (2014)	Y	Y	N	Y	Y	N	N/A	Y	Y	Y	Y
Wittchen (2012)	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y
Carvalho-Pinto (2017)	N	Y	N	Y	Y	N	N/A	Y	Y	Y	Y

Note. RELEVANT = Real Life Evidence Assessment Tool, N = does not meet the criterion, Y = meets the criterion, N/A = not applicable, * = exposure to omalizumab described but no doses reported, † = reference 32, ‡ = reference 33

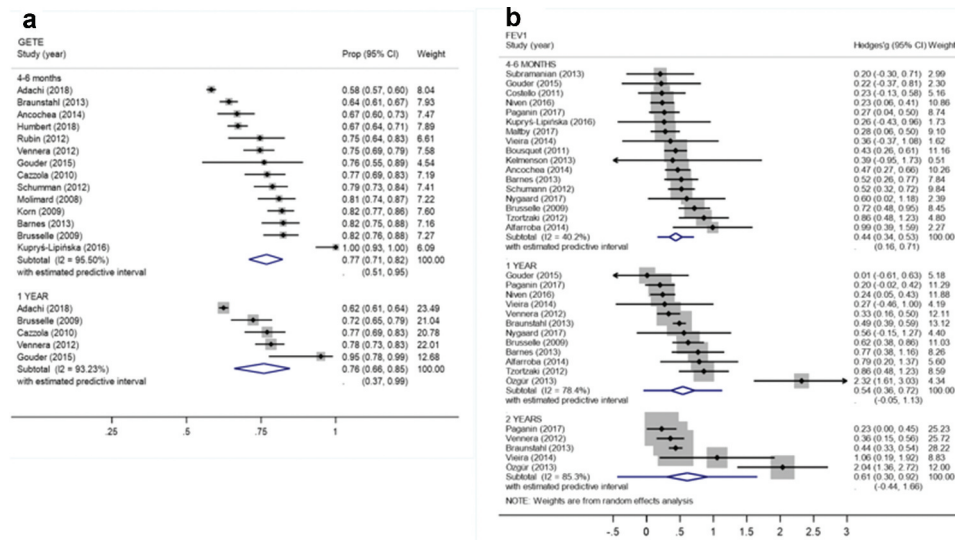


Figure 2. A. Pooled estimates of proportions of patients with Global evaluation of treatment effectiveness (GETE) of good to excellent. B. Improvements in forced expiratory volume in 1 second (of percent predicted). CI = confidence interval, FEV1 = forced expiratory volume in 1 second. Prop = proportion of participants with GETE rating of good to excellent. Braunstaht (2013) refers to reference 32.

3.2. Forced expiratory volume in 1 second

Data on FEV₁ were available for 1706 participants at 4–6 months, 1632 participants at 1 year, and 965 participants at 2 years after initiation of omalizumab **Figure 2**. There were moderate improvements in FEV₁ at 4–6 months (Hedges' $g = 0.44$), 1 year (Hedges' $g = 0.54$) and 2 years (Hedges' $g = 0.61$) compared to enrollment values. These improvements were equivalent to mean improvements of 8.04% (95% CI [6.24, 9.84]), 10.4% (95% CI [7.06, 13.75]), and 10.61% (95% CI [5.79, 15.45]) (percent of expected) at 4–6 months, 1 year, and 2 years, respectively. There was significant heterogeneity among the studies at each time point. Analyses were run a second time after excluding the results reported by Özgür and colleagues, as the sample appeared to be an outlier. Removal of these findings resulted in less heterogeneity and more precise estimates (1 year: Hedges' $g = 0.45$, 95% CI [0.32,

0.58], $z = 6.67$, $p < .001$, $I^2 = 59.1\%$, $p = .007$; 2 years: Hedges' $g = 0.38$, 95% CI [0.24, 0.52], $z = 5.28$, $p < .001$, $I^2 = 42.3\%$, $p = .158$). Comparison of effect sizes using random effect meta-regression revealed no significant difference in effect sizes by research design ($p = 0.58$ at 4–6 months, $p = 0.25$ at 1 year, $p = 0.28$ at 2 years).

3.3. Asthma-related quality of life (AQLQ)

Data on AQLQ scores were available for 931 participants at 4–6 months and 389 at 1 year after starting treatment with omalizumab **Figure 3**. Compared to scores obtained at enrollment, large improvements in AQLQ were noted at 4–6 months (Hedges' $g = 1.03$) and 2 years (Hedges' $g = 1.11$) after beginning therapy. These corresponded with improvements of 1.39 (95% CI [1.18, 1.61]) points on the AQLQ at 4–6 months and

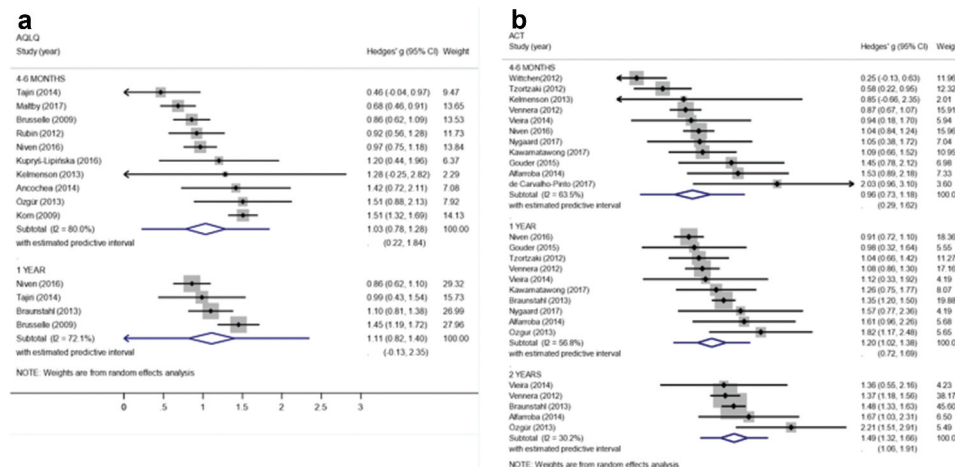


Figure 3. A. Improvements in score on the asthma-related quality-of-life questionnaire (AQLQ). B. Improvements in Asthma Control Test (ACT). CI = confidence interval. Braunstaht (2013) refers to reference 32.

1.42 (95% CI [1.13, 1.72]) points on the AQLQ at 1 year. Significant heterogeneity among the studies was noted at both time points. Effect sizes were not statistically different based on research design at 4–6 months ($p = 0.17$). All studies evaluating AQLQ at 1 year were prospective, so no comparison of effect sizes by design could be conducted.

3.4. Asthma control (ACT)

Data on ACT scores were available for 643 participants at 4–6 months, 931 participants at 1 year, and 694 at 2 years after the onset of treatment Figure 3. Omalizumab had a large effect on ACT scores after 4–6 months (Hedges' $g = 0.96$), 1 year (Hedges' $g = 1.20$), and 2 years (Hedges' $g = 1.49$). These were equivalent to improvements of 4.82 (95% CI [3.64, 6.01]), 5.73 (95% CI [4.89, 6.58]), and 7.04 (95% CI [5.98, 8.10]) points on the ACT at 4–6 months, 1 year, and 2 years, respectively. Between-study heterogeneity was significant and moderate at 4–6 months and 1 year after initiating omalizumab but was not significant at 2 years. No significant differences in effect size based on research design were noted at 4–6 months ($p = 0.84$), 1 year ($p = 0.21$) or 2 years ($p = 0.15$).

3.5. Oral and inhaled corticosteroids

Data on oral corticosteroid use were available for 964 participants at 4–6 weeks, 1456 participants at 1 year, and 666 participants at 2 years after starting therapy with omalizumab Figure 4. The likelihood of taking oral corticosteroids dropped by 44% after 4–6 months, 33% after 1 year, and 52% after 2 years of treatment. Significant between-study heterogeneity was observed at 4–6 months and 1 year but not at 2 years. Comparisons of effect sizes by research design revealed no significant differences at 4–6 months ($p = 0.18$), 1 year ($p = 0.83$) or 2 years ($p = 0.75$).

Data on the mean dose of inhaled corticosteroids were available for 403 participants at 4–6 months, 488 participants at 1 year, and 150 participants at 2 years after the onset of

treatment Figure 4. Reductions in the mean dose of inhaled corticosteroids were small after 4–6 months of treatment (Hedges' $g = 0.32$), but got progressively larger at 1 year (Hedges' $g = 0.41$) and 2 years (Hedges' $g = 0.58$) after starting omalizumab. Reductions in inhaled corticosteroid dosages were equivalent to reductions of 135.01 (95% CI [72.59, 197.44]), 291.42 (95% CI [129.89, 452.96]), and 432.94 (95% CI [183.45, 682.43]) beclomethasone equivalents at 4–6 months, 1 year, and 2 years, respectively. Between-study heterogeneity was not significant at any time point. No significant differences in effect sizes due to research design were observed at 4–6 months ($p = 0.44$), 1 year ($p = 0.81$) or 2 years ($p = 0.38$).

3.6. Asthma exacerbations

Data on the mean number of asthma exacerbations were available for 5270 participants at 1 year and 761 participants at 2 years after beginning therapy with omalizumab Figure 5. Large reductions in the mean number of asthma exacerbations were noted at 1 year (Hedges' $g = 0.84$) and 2 years (Hedges' $g = 1.04$) following initiation of treatment with omalizumab compared with the prior year. This was equivalent to mean reductions of 2.75 (95% CI [2.10, 3.40]) exacerbations at 1 year and 3.17 (95% CI [1.74, 4.60]) exacerbations at 2 years. Considerable significant between-study heterogeneity was observed at 1 year. Heterogeneity also was significant at 2 years but was considerably smaller. The effect of omalizumab on exacerbations was not statistically different when compared by research design ($p = 0.56$ at 4–6 months, $p = 0.43$ at 1 year, $p = 0.62$ at 2 years).

3.7. Asthma-related hospitalizations

Data on the mean number of asthma-related hospitalization were available for 3979 participants at 1 year after beginning treatment Figure 5. There were moderate reductions in the mean number of asthma-related hospitalizations at 1 year (Hedges' $g = 0.35$) that were equivalent to a mean reduction of 0.72 (95% CI [0.36, 1.07]) days. There was moderate significant heterogeneity among the samples. No significant

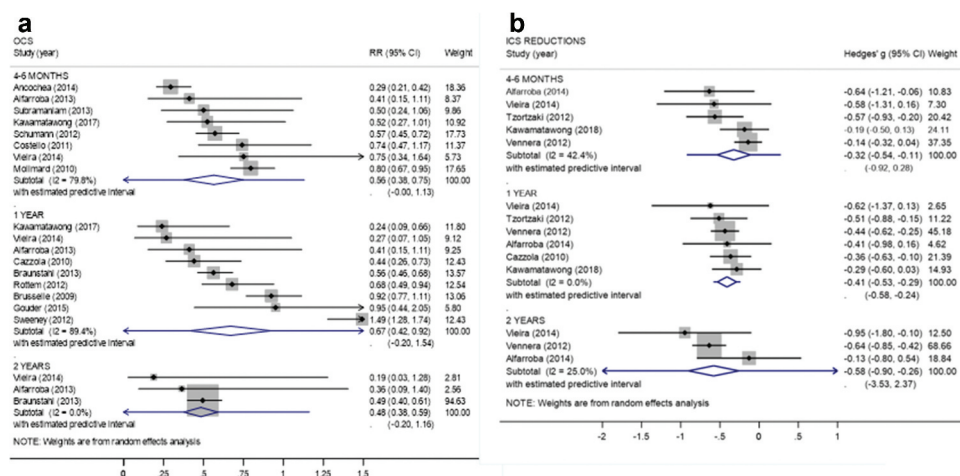


Figure 4. A. Reductions in proportion of patients using oral corticosteroids. Dropping Sweeney from 1 year analysis resulted in less heterogeneity and more precise estimates (1 year: RR = 0.59, 95% CI [0.44, 0.80], $z = 3.41$, $p = .001$, $IC = 74.3\%$, $p < .001$). Braunstaal (2013) refers to reference 33. B. Reductions in proportion of patients taking inhaled corticosteroids (beclomethasone equivalents). ICS = inhaled corticosteroids, OCS = oral corticosteroids, RR = relative risk.

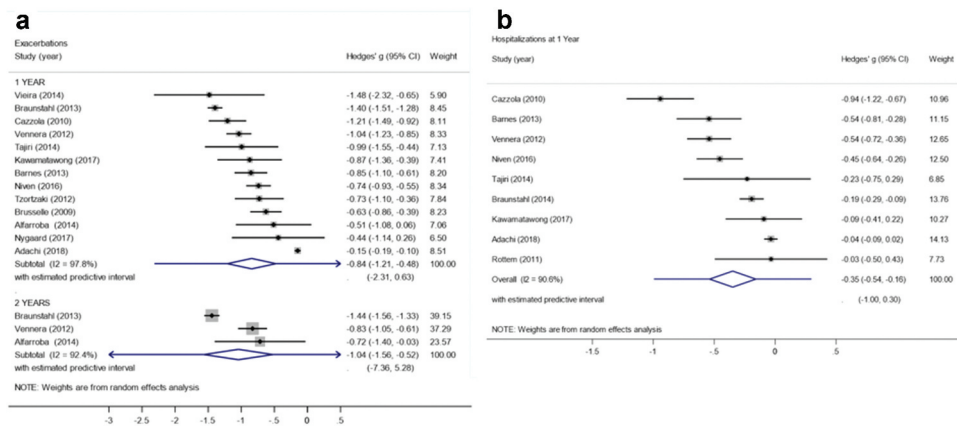


Figure 5. A. Reduction in mean number of asthma exacerbations. Braunstahl (2013) refers to reference 32. B. Reduction in the mean number of asthma-related hospitalizations at 1 year. CI = confidence interval.

difference in effect size was observed when compared using random effect meta-regression ($p = 0.55$).

3.8. Adverse events

Data on the proportion of patients who experienced an adverse event were available for 761 patients at 4–6 months and 4025 patients at 1 year after enrollment **Figure 6**. On average, 20% of the patients experienced an adverse event within the first 6 months of enrollment and 33% of the patients experienced an adverse event within the first year of enrollment. There was considerable heterogeneity among the studies. Comparison of effect sizes by research design at 4–6 months revealed no significant association ($p = 0.59$). All studies evaluating adverse

events at 1 year were prospective, so comparison of effect size by research design was not possible.

4. Discussion

Randomized controlled trials are often considered the 'gold standard' against which other research is compared. However, noncontrolled studies of individuals in treatment settings provide 'real-world' data on the effectiveness of medications such as omalizumab. This meta-analysis of 'real-world' data on omalizumab effectiveness builds on previous findings by including data from 14 new articles. These 14 articles are a blend of prospective and retrospective studies of adults with acute allergic asthma conducted in Asia, Australia, South America, and Europe. The pooled effect sizes generated from these studies reinforce our

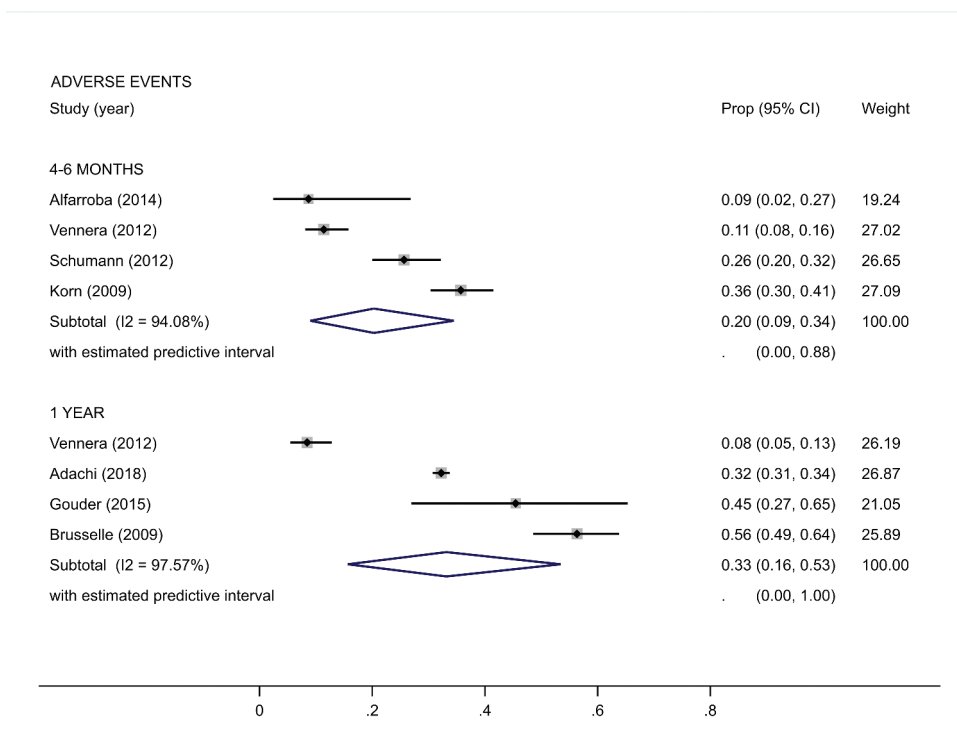


Figure 6. Pooled estimates of proportions of patients with adverse events. CI = confidence interval, Prop = proportion of patients with an adverse event.

conclusion that treatment with omalizumab improves objective and subjective outcomes in patients with severe allergic asthma. Consistently, treatment with omalizumab resulted in better GETE scores, higher FEV₁, better self-reported quality-of-life as measured by AQLQ, better asthma control as measured by ACT, fewer patients on oral corticosteroids, lower doses of inhaled corticosteroids, and fewer exacerbations and hospitalizations associated with asthma.

Considerable between-study heterogeneity was observed in each of these meta-analyses. Removal of one case often reduced between-study heterogeneity but rarely was between-study heterogeneity non-significant or less than moderate after removal of one case. There are several possible explanations for the observed between-study heterogeneity. Many of these studies were conducted in different countries, so differences in sample characteristics may contribute to some between-study heterogeneity. All were performed in different clinical settings, as well. Differences in health-care delivery systems and treatment protocols also may contribute to some of the between-study heterogeneity. Although there is considerable between-study heterogeneity, it should not be viewed as a limitation. The studies included in this meta-analysis were not under the same restrictions imposed by randomized controlled trials, so heterogeneity is expected [69]. If this were a meta-analysis of randomized controlled trials to evaluate the efficacy of a medication, heterogeneity would be more concerning.

The findings of our previous meta-analysis are refined by the addition of new research in this meta-analysis. As before, three-quarters of the participants had a GETE rating of good or excellent at 4–6 months and 1 year after beginning treatment with omalizumab. Clinical measures of asthma severity (FEV₁, OCS use, mean dose of ICS) were moderately better 4–6 months after initiation of treatment. Mean dose of ICS and mean FEV₁% of predicted demonstrated consistent, progressive improvement throughout the 2 years. The mean number of exacerbations and asthma-associated hospitalizations improved in response to omalizumab, as well. The mean number of exacerbations was moderately lower 1 year after starting omalizumab and the effect grew progressively larger at 2 years after beginning treatment. There also was a small reduction in the mean number of asthma-associated hospitalizations 1 year after beginning treatment.

Patient-reported asthma control and quality-of-life also improved after initiating omalizumab. Improvements in patient-reported asthma severity were greater than those observed for the clinical measures of asthma severity. There were large improvements in AQLQ and ACT scores 4–6 months after starting therapy. Improvements in quality-of-life and asthma control grew larger at 1 year and 2 years when compared with enrollment values.

Although these findings support the effectiveness of omalizumab, consideration should be given to the potential harms associated with omalizumab. The results of this meta-analysis indicate that one-fifth of patients on omalizumab will experience an adverse event in the first 6 months and one-third will experience an adverse event in the first year of omalizumab

therapy. Clinicians and patients should be aware of the potential adverse events so they can be addressed should they arise.

4.1. Limitations

Many of the participants in the included studies were recruited from different countries with unique health systems yet the analysis treated the participants as though they were a homogenous group. Different environments and health-care systems may contribute to heterogeneity in omalizumab effectiveness. Stratification of studies by geographic location or similar health-care systems might uncover some unexplained heterogeneity observed in this analysis.

All of the studies included in this meta-analysis had at least one 'fatal flaw' according to the RELEVANT criteria and some studies had more than one. Most of the researchers who designed these studies failed to include a comparison group of individuals who were not taking omalizumab. Many researchers acknowledged that other factors may have contributed to the findings, but few formally evaluated the effects of confounding variables. Effectiveness studies that take place in 'real-world' settings often are not subject to the same degree of rigor as randomized controlled trials. However, to increase the likelihood that observed effects are due to the intervention rather than confounding variables, future research on the effectiveness of omalizumab in 'real-world' settings should include more rigorous control.

4.2. Implications for research

The current meta-analysis provides 'real-world' evidence that omalizumab is associated with improvement in several measures of asthma severity but additional research is needed. Little is known about whether improvements in asthma severity are sustained beyond 2 years. To determine if improvements are maintained, future research should explore the effect of omalizumab on measures of asthma severity for longer periods of time. The effect of omalizumab on asthma-associated outcomes may not be constant, and insights gained from this meta-analysis rely on data from patients who remain on omalizumab in these individual studies. Steady improvements over time were observed for several outcome variables, but the rate of improvement has not been explicated. There is evidence that omalizumab is effective at treating other conditions, including atopic dermatitis and nasal polyposis [70,71]. Clinicians may consider the overlapping benefits of omalizumab in the treatment of multiple comorbid diseases when determining plans of care. To help clinicians determine if omalizumab would be effective at treating multiple comorbid conditions, meta-analyses of omalizumab effectiveness in other conditions should be completed. Finally, mortality was not included as an outcome in this meta-analysis. Establishing the effect of omalizumab on mortality rates would provide information necessary for the support of omalizumab as a treatment for severe asthma.

5. Expert opinion

In conclusion, across studies conducted in uncontrolled environments, omalizumab is an effective adjuvant treatment for severe asthma. Moderate improvements in clinical indicators of asthma severity, including FEV1 and medication use, are observed up to 2 years following the onset of treatment. Moderate improvements in asthma exacerbations and asthma-associated hospitalizations also are observed. Improvements in patient-reported asthma control and quality-of-life are much larger and continue to improve after 1 year of treatment. The findings of this meta-analysis support the addition of omalizumab in the treatment of severe asthma.

Funding

This paper was not funded.

Declaration of interest

K MacDonald and I Abraham are associates of and hold equity in Matrix45. However, this meta-analysis was not funded by Matrix45 or any other entity. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Funding

This paper was not funded.

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