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# Real-World Effectiveness of Omalizumab in Severe Allergic Asthma: A Meta-Analysis of Observational Studies



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Montpellier, Le Kremlin-Bicêtre, and Le Plessis-Robinson, France; Berlin, Germany; Newcastle, NSW, Australia; Ioannina, Greece; and Basel, Switzerland

**What is already known about this topic?** Omalizumab, an anti-IgE monoclonal antibody, has been shown to be effective and safe in patients with moderate-to-severe allergic asthma in both randomized and real-world studies.

**What does this article add to our knowledge?** Add-on omalizumab consistently improved treatment effectiveness, lung function, and patient-reported outcomes, and reduced the rate of severe exacerbations, oral corticosteroid use, health care resource utilization, and school/workdays absenteeism in real-life settings.

**How does this study impact current management guidelines?** This meta-analysis of real-world data demonstrated the effectiveness of omalizumab in the real-life practice.

**BACKGROUND:** Assessment of clinical outcomes in the real-world corroborates findings from randomized controlled trials (RCTs).

**OBJECTIVE:** This meta-analysis evaluated real-world data of omalizumab on treatment response, lung function, exacerbations, oral corticosteroid (OCS) use, patient-reported outcomes (PROs), health care resource utilization (HCRU), and school/work absenteeism at 4, 6, and 12 months after treatment.

**METHODS:** Observational studies in patients with severe allergic asthma ( $\geq 6$  years) treated with omalizumab for  $\geq 16$  weeks, published from January 2005 to October 2018, were retrieved from PubMed, Embase, and Cochrane. A random-effects model was used to assess heterogeneity.

**RESULTS:** In total, 86 publications were included. Global evaluation of treatment effectiveness (GETE) was good/excellent in 77% patients at 16 weeks (risk difference: 0.77; 95% confidence interval [CI]: 0.70-0.84;  $I^2 = 96\%$ ) and in 82% patients at 12 months (0.82, 0.73-0.91; 97%). The mean improvement in forced expiratory volume in 1 second was 160, 220, and 250 mL at 16 weeks, 6 months, and 12 months, respectively. There was a decrease in Asthma Control Questionnaire score at 16 weeks ( $-1.14$ ), 6 months ( $-1.56$ ), and 12 months ( $-1.13$ ) after omalizumab therapy. Omalizumab significantly reduced annualized rate of severe exacerbations (risk ratio [RR]: 0.41, 95% CI: 0.30-0.56;  $I^2 = 96\%$ ), proportion of patients receiving OCS (RR: 0.59, 95% CI: 0.47-0.75;  $I^2 = 96\%$ ), and number of

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*Abbreviations used*

ACQ- Asthma Control Questionnaire  
ACT- Asthma Control Test  
AQLQ- Asthma Quality of Life Questionnaire  
CI- Confidence interval  
ER- Emergency room  
FEV<sub>1</sub>- Forced expiratory volume in 1 second  
GETE- Global evaluation of treatment effectiveness  
HCRU- Health care resource utilization  
ICS- Inhaled corticosteroid  
MCID- Minimal clinically important difference  
MD- Mean difference  
OCS- Oral corticosteroid  
PRO- Patient-reported outcome  
RCT- Randomized controlled trial  
RD- Risk difference  
RR- Risk ratio  
RWD- Real-world data  
SAA- Severe allergic asthma

unscheduled physician visits (mean difference:  $-2.34$ , 95% CI:  $-3.54$  to  $-1.13$ ;  $I^2 = 98\%$ ) at 12 months versus baseline.

**CONCLUSION:** The consistent improvements in GETE, lung function, and PROs, and reductions in asthma exacerbations, OCS use, and HCRU with add-on omalizumab in real-life confirm and complement the efficacy data of RCTs. © 2021 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2021;9:2702-14)

**Key words:** Omalizumab; Severe allergic asthma; Real-world evidence; Meta-analysis; Global evaluation of treatment effectiveness; Severe exacerbations; Lung function; Health care resource utilization; Patient-reported outcomes

Omalizumab, the recombinant monoclonal antibody against IgE, was approved for patients with moderate-to-severe allergic asthma uncontrolled despite treatment with high-dose controller medications. Although several randomized controlled trials (RCTs) have demonstrated the efficacy and safety of omalizumab,<sup>1-6</sup> they were performed under optimized conditions and stringent inclusion and exclusion criteria, which do not reflect medical practice in the real-world settings. Moreover, RCTs enroll a narrow, smaller subset of patients limiting the extrapolation of the findings to the more heterogeneous patient population encountered in routine clinical practice.<sup>7</sup> Furthermore, medication adherence, the key pillar for treatment effectiveness, is closely monitored in RCTs, which is not always the case in real-world settings.<sup>7</sup> Therefore, alternative designs such as pragmatic open-label RCTs and observational studies are needed to address these gaps between RCTs and real-world evidence.

After the approval of omalizumab, several real-world studies<sup>8</sup> have been initiated that led to its wide use with more than 1.3 million patient-years of exposure (Unpublished data, Omalizumab Periodic Safety Report [PSUR], Novartis). A systematic review of 24 real-world observational studies in adult patients with severe allergic asthma (SAA) has shown the short- and long-term efficacy of

omalizumab by improving lung function, asthma symptoms, and quality of life, and reduced co-medication, severe exacerbations, school/workdays lost, and health care resource utilization (HCRU) with benefits extending up to 2 to 4 years after therapy.<sup>8</sup> A meta-analysis conducted on these noncontrolled studies demonstrated the real-life pharmacotherapeutic effectiveness of omalizumab and complemented the efficacy data from RCTs.<sup>9</sup> More recently, a systematic review of 42 real-world studies of omalizumab in patients over 12 years confirmed the long-term effectiveness beyond 4 years.<sup>10</sup> However, to date, no meta-analysis has summarized the real-world effectiveness of omalizumab in patients  $\geq 6$  years in terms of global evaluation of treatment effectiveness (GETE), lung function, asthma exacerbations, oral corticosteroid (OCS) use, patient-reported outcomes (PROs), HCRU, and school/work absenteeism. The aim of this analysis was to assess the efficacy of omalizumab based on these outcome measures in patients with SAA.

## METHODS

### Information sources and study selection

A systematic literature search was conducted in the PubMed, Embase, and Cochrane Controlled Trials Register (CENTRAL) databases, to identify publications of observational studies on omalizumab in patients aged  $\geq 6$  years with SAA, published from January 2005 to October 2018. The medical subject headings and search terms used were “omalizumab” OR “Xolair” AND “asthma,” with studies filtered by clinical trial, publication type, and language. In addition, a search for relevant unpublished studies was performed using the same search terms in [ClinicalTrials.gov](http://ClinicalTrials.gov), the Novartis clinical trials database ([www.novartisclinicaltrials.com](http://www.novartisclinicaltrials.com)), and the clinical trial databases of GSK (<https://www.gsk-studyregister.com>), Pfizer (<https://www.pfizerpro.com/clinical-trials>), and AstraZeneca (<https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Search>). Publications and studies identified were manually reviewed, using specific inclusion criteria presented below. Other potential studies were identified through manual searching of the eligible studies.

- (1) Population: patients aged  $\geq 6$  years with SAA and a minimum of 12 months' pre-omalizumab data and 16-week to 1-year post-treatment data.
- (2) Intervention: omalizumab for treatment of SAA.
- (3) Comparator: omalizumab effectiveness was compared with 12 months' pre-omalizumab data.
- (4) Outcomes: studies with at least one of the following outcomes were included: physician-rated treatment effectiveness (by GETE), lung function, annualized rate of severe exacerbations, OCS use, PROs (Asthma Control Questionnaire [ACQ], Asthma Control Test [ACT], and Asthma Quality of Life Questionnaire [AQLQ]), HCRU (asthma-related hospital admissions, emergency room [ER] visits, and unscheduled physician visits), and school or work absenteeism.
- (5) Study design: observational studies.

### Data extraction

Two reviewers independently assessed each study based on the predefined eligibility criteria and extracted data from eligible studies. Patient demographics and clinical characteristics (including age, gender, race, smoking status, body weight, and duration of asthma) and outcomes data were extracted from all included studies. Literature search and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines.<sup>11</sup>

## Outcomes

The primary outcome of interest in this meta-analysis was physicians' GETE, a validated PRO, which measures the overall response to treatment on a 5-point scale of excellent, good, moderate, poor, or worsening. GETE responders were defined as those with an excellent or good response, whereas nonresponders were those with moderate, poor, or worsening response (Online Repository text at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). The secondary outcomes reported were the mean change in forced expiratory volume in 1 second (FEV<sub>1</sub>), annualized rate of severe exacerbations, OCS use, PROs (ACQ, ACT, and AQLQ), HCRU (hospitalizations, ER visits, and unscheduled physician visits), and school or work absenteeism, each evaluated 16 weeks, 6 months, and 12 months after omalizumab therapy.

Quality and risk of bias of individual studies was not assessed in this meta-analysis. Furthermore, no sensitivity or subgroup analysis was performed.

## Summary measures and synthesis of results

Binary outcomes were presented as risk difference (RD) or risk ratio (RR) and 95% confidence intervals (CI), whereas continuous outcomes were presented as mean difference (MD) and 95% CI. To make the optimal use of extracted data and to avoid effect size selection bias, the effect measures in the analysis were analyzed using a random-effects model for all outcomes, as the included studies differed in the mixes of participants and to address the clinical heterogeneity variation across studies. Also, as the included studies differed in treatment duration, we analyzed the effect measures as 16 weeks/4 months, and 6 and 12 months to normalize the effect sizes. Heterogeneity was assessed and quantified using I<sup>2</sup> statistics with upper limits of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively.<sup>12</sup> Studies were weighted using the DerSimonian and Laird random-effects model.<sup>13</sup>

The effect estimate for the primary outcome of interest (GETE) obtained in the meta-analysis of observational studies was also compared with the response rate for GETE in the individual RCTs (EXALT,<sup>14</sup> EXTRA,<sup>15</sup> and INNOVATE<sup>4</sup>). A generalized linear mixed model was applied assuming a binomial distribution for GETE responders across the RCTs and the GETE responder rate from meta-analysis, to observe whether the 95% CI for the response rates overlaps, which would indicate that the response rate for GETE obtained in RCT versus meta-analysis is comparable. The model accounted for overdispersion, which may occur because of differences in studies/population/other intrinsic factors by using a nonparametric random residual approach. The model provided an estimate of the pooled (average) response that was then compared with the results of individual RCTs and the meta-analysis estimate, to assess whether GETE response rates are comparable across the RCTs versus meta-analysis. Analysis was performed using R software (version 3.4.1, Meta package).<sup>16</sup>

## RESULTS

### Study selection

A total of 2019 publications were identified from the databases. Of these, 626 duplicate publications were excluded. A total of 1393 publications were retained and screened manually, of which 651 were rejected based on language restrictions, because they were conference abstracts, or due to disease, and relevancy. Of the remaining 742 publications, 614 were excluded based on study design (most of these were RCTs, reviews, letters, *post hoc* analysis), and a further 52 publications were ineligible

based on outcomes. Seventy-six eligible studies therefore remained. A further 10 studies were identified by manual review of these articles, and a total of 86 publications were included in this meta-analysis.<sup>1,14,17-100</sup> Eighty-four studies were identified from the literature databases, and 2 unpublished studies were identified from the [ClinicalTrials.gov](http://ClinicalTrials.gov) and manufacturer databases (Figure 1).

### Baseline demographics and clinical characteristics

Baseline demographics are presented in Table E1 (available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Most studies were observational in nature, but 4 randomized, open-label studies were also included as these studies mirrored real-life clinical practice. The studies included patients across age groups ( $\geq 6$  years) and gender. Although majority of studies included white/Caucasian population, few studies also included black, Asians, and other races.

### Global evaluation of treatment effectiveness

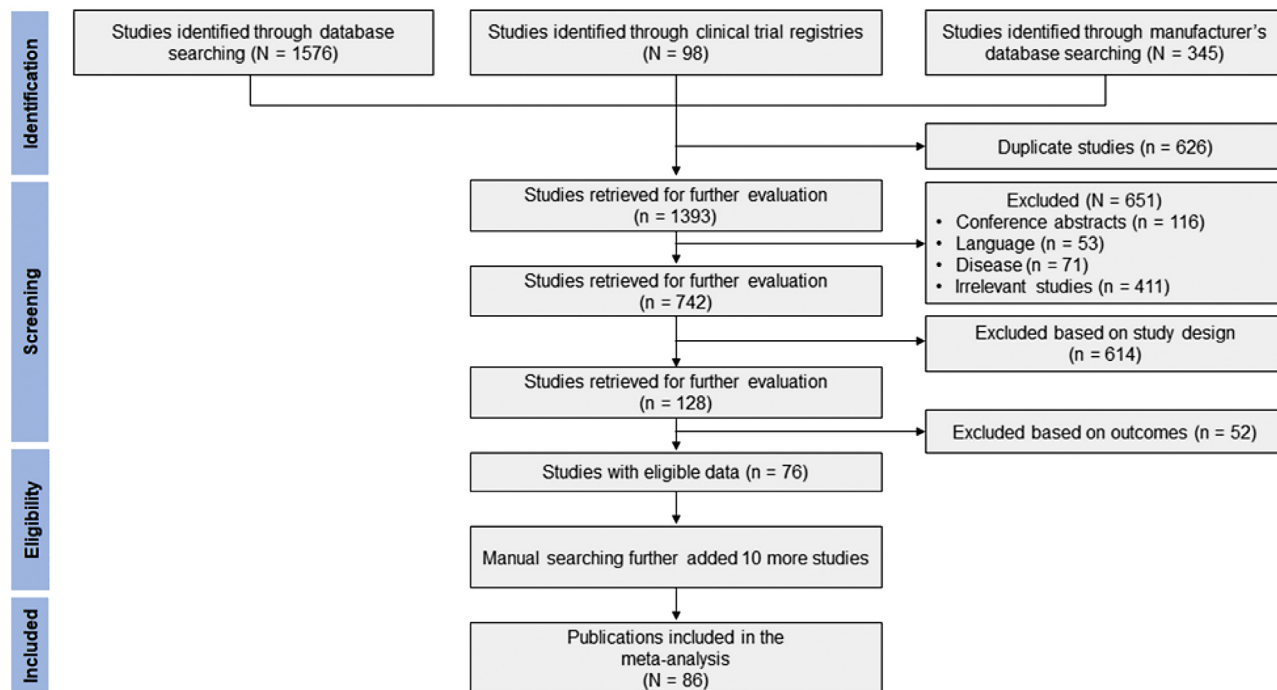
GETE data were available from 15 publications with 5976 patients after 16 weeks of therapy, 2 studies with 1052 patients after 6 months, and 10 studies with 3410 patients after 12 months. On average, 77% patients achieved a good or excellent GETE response after 16 weeks (RD: 0.77, 95% CI: 0.70-0.84;  $P < .01$ , I<sup>2</sup> = 96%), and the effect continued with 82% of patients at 12 months (RD: 0.82, 95% CI: 0.73-0.91;  $P < .01$ ), with considerable heterogeneity (I<sup>2</sup> = 97%; Figure 2). Despite this heterogeneity, the GETE responses were consistently positive (Figure 2).

### Forced expiratory volume in 1 second

Data on FEV<sub>1</sub> were available from 5 studies with 548 patients after 16 weeks, 3 studies with 217 patients after 6 months, and 5 studies with 260 patients after 12 months of treatment (Figure 3). Omalizumab significantly improved FEV<sub>1</sub> with mean change from baseline of 160 mL at 16 weeks (95% CI: 0.04-0.28;  $P < .01$ , I<sup>2</sup> = 25%), 220 mL at 6 months (95% CI: 0.08-0.36;  $P < .01$ , I<sup>2</sup> = 0%), and 250 mL at 12 months (95% CI: 0.03-0.48;  $P = .02$ , I<sup>2</sup> = 50%) with moderate heterogeneity.

**Severe exacerbations.** Data for annualized rate of severe exacerbations were available from 7 publications with 4135 patients after 12 months of therapy. Omalizumab reduced the risk by 81% (RR [95% CI]: 0.19 [0.09-0.41];  $P < .01$ , I<sup>2</sup> = 87%) and 59% (RR [95% CI]: 0.41 [0.30-0.56];  $P < .01$ , I<sup>2</sup> = 96%) after treatment for 16 weeks and 12 months, respectively (Figure 4). Data on change in the mean number of severe exacerbations were available from 7 publications with a total of 1208 patients after 16 weeks, 6 publications with a total of 1190 patients after 6 months, and 19 publications with a total of 4286 patients after 12 months of omalizumab therapy. The number of severe exacerbations decreased significantly with the MD of 2.13 (MD [95% CI]: -2.13 [-2.94 to -1.32];  $P < .01$ , I<sup>2</sup> = 97%), 2.75 (MD [95% CI]: -2.75 [-3.74 to -2.02];  $P < .01$ , I<sup>2</sup> = 82%), and 2.75 (MD [95% CI]: -2.75 [-3.46 to -2.04];  $P < .01$ , I<sup>2</sup> = 98%) at 16 weeks, 6 months, and 12 months, respectively, after initiation of treatment compared with baseline (Figure 5).

**OCS-sparing effect.** Data on OCS sparing effect were available from 7 studies with a total of 4706 patients after 16 weeks and from 18 studies with a total of 8279 patients after 12 months of therapy. Treatment with omalizumab significantly



**FIGURE 1.** Preferred Reporting Items for Systematic Reviews and Meta-analysis flow diagram. The core and extension studies by Odajima et al were considered as 2 separate publications bringing the total number of publications to 86.

reduced the proportion of patients receiving OCS by 32% (RR [95% CI]: 0.68 [0.57-0.82];  $P < .01$ ,  $I^2 = 83%$ ) and 41% (RR [95% CI]: 0.59 [0.47-0.75];  $P < .01$ ,  $I^2 = 95%$ ) at 16 weeks and 12 months, respectively, compared with baseline (Figure 6). Of the patients treated with omalizumab, a reduction of  $\geq 20%$  in OCS dose from baseline was observed in 50% patients at 16 weeks, 43% at 6 months, and 57% at 12 months (Figure E1, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). The mean daily OCS dose reduced by 6.64 mg/day (MD [95% CI]: -6.64 [-8.11 to -5.17];  $P < .01$ ,  $I^2 = 19%$ ) and 5.45 mg/day (MD [95% CI]: -5.45 [-9.91 to -0.98];  $P = .02$ ,  $I^2 = 90%$ ) after treatment for 16 weeks and 12 months, respectively (Figure E2, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).

### Asthma control and patient-reported outcomes

**Asthma Control Questionnaire.** ACQ data were available from 5 publications with a total of 565 patients at 16 weeks, 5 publications with a total of 623 patients at 6 months, and 3 publications with a total of 194 patients at 12 months of therapy. A decrease in ACQ score was observed at 16 weeks (MD [95% CI]: -1.14 [-1.40 to -0.89];  $I^2 = 74%$ ), 6 months (MD [95% CI]: -1.56 [-1.66 to -1.45];  $I^2 = 0%$ ), and 12 months (MD [95% CI]: -1.13 [-1.47 to -0.79];  $I^2 = 67%$ ) after omalizumab therapy ( $P < .01$  at all time points; Figure 7).

**Asthma Control Test.** ACT score were available from 8 publications with a total of 582 patients at 16 weeks, 6 publications with a total of 1047 patients at 6 months, and 22 publications with a total of 2669 patients at 12 months after omalizumab therapy. ACT score significantly improved after omalizumab treatment at 16 weeks (MD [95% CI]: 4.44 [3.55-

5.34];  $I^2 = 71%$ ), 6 months (MD [95% CI]: 3.98 [2.74-5.23];  $I^2 = 82%$ ), and 12 months (MD [95% CI]: 6.47 [4.76-8.18];  $I^2 = 98%$ ; Figure E3, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).

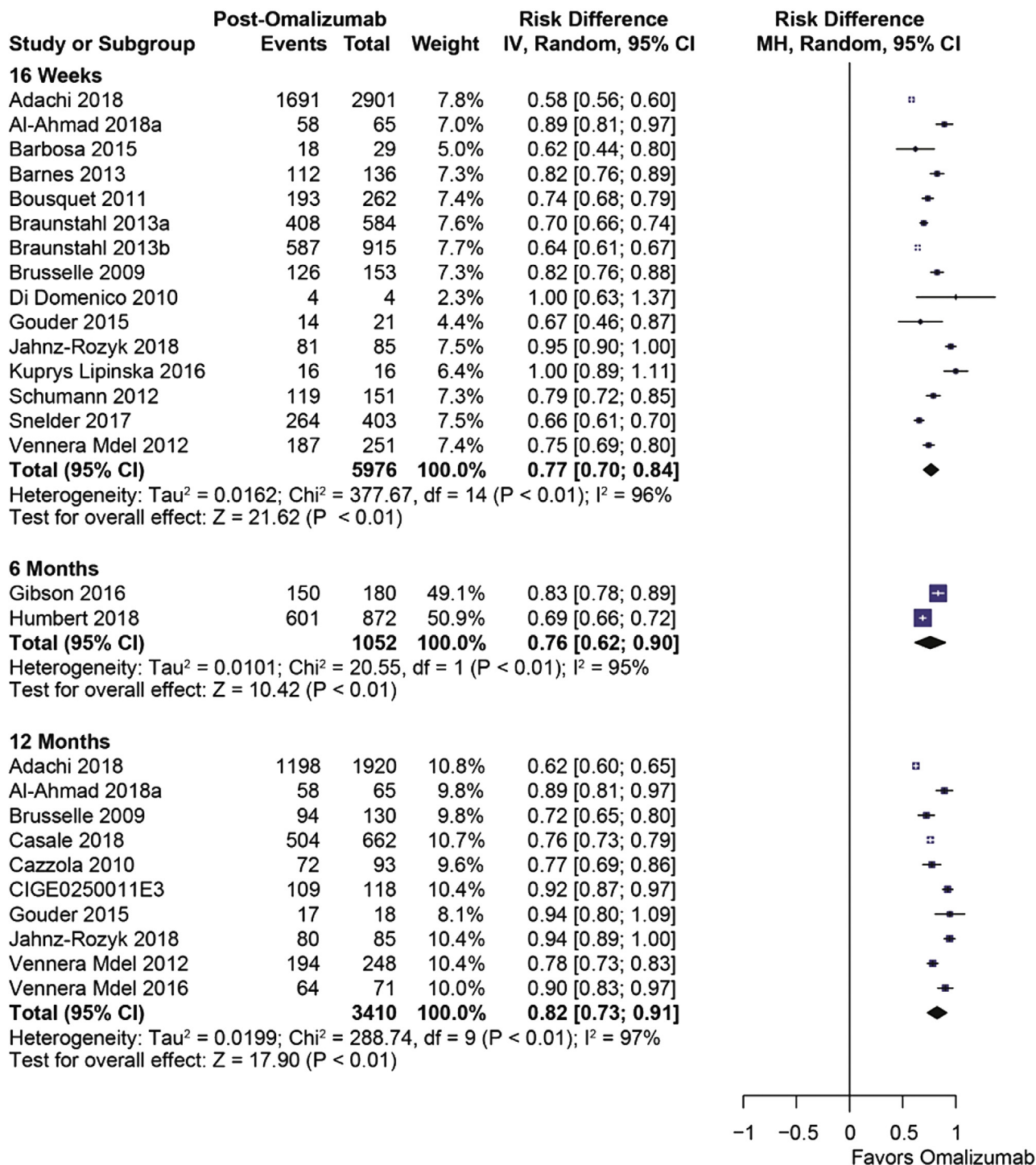
**Asthma Quality of Life Questionnaire.** Data on AQLQ score were available from 5 studies with a total of 333 patients at 16 weeks, 454 patients at 6 months, and 375 patients at 12 months after omalizumab treatment. The change in AQLQ score from baseline was 1.10 at 16 weeks (MD [95% CI]: 1.10 [0.85-1.36];  $I^2 = 40%$ ), 1.13 at 6 months (MD [95% CI]: 1.13 [0.73-1.54];  $I^2 = 85%$ ), and 1.44 at 12 months (MD [95% CI]: 1.44 [1.16-1.72];  $I^2 = 64%$ ) after omalizumab therapy ( $P < .01$  at all time points; Figure E4, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). These data demonstrate improved asthma control as well as quality of life after omalizumab therapy in patients with SAA.

### School or work absenteeism

Data on school or work absenteeism were available from 6 publications and a total of 3997 patients after 12 months of therapy (Figure E5, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). The missed school or workdays were numerically reduced by 2.12 days on treatment with omalizumab at 12 months (MD [95% CI]: -2.12 [-4.79 to 0.55];  $P = .12$ ).

### Health care resource utilization

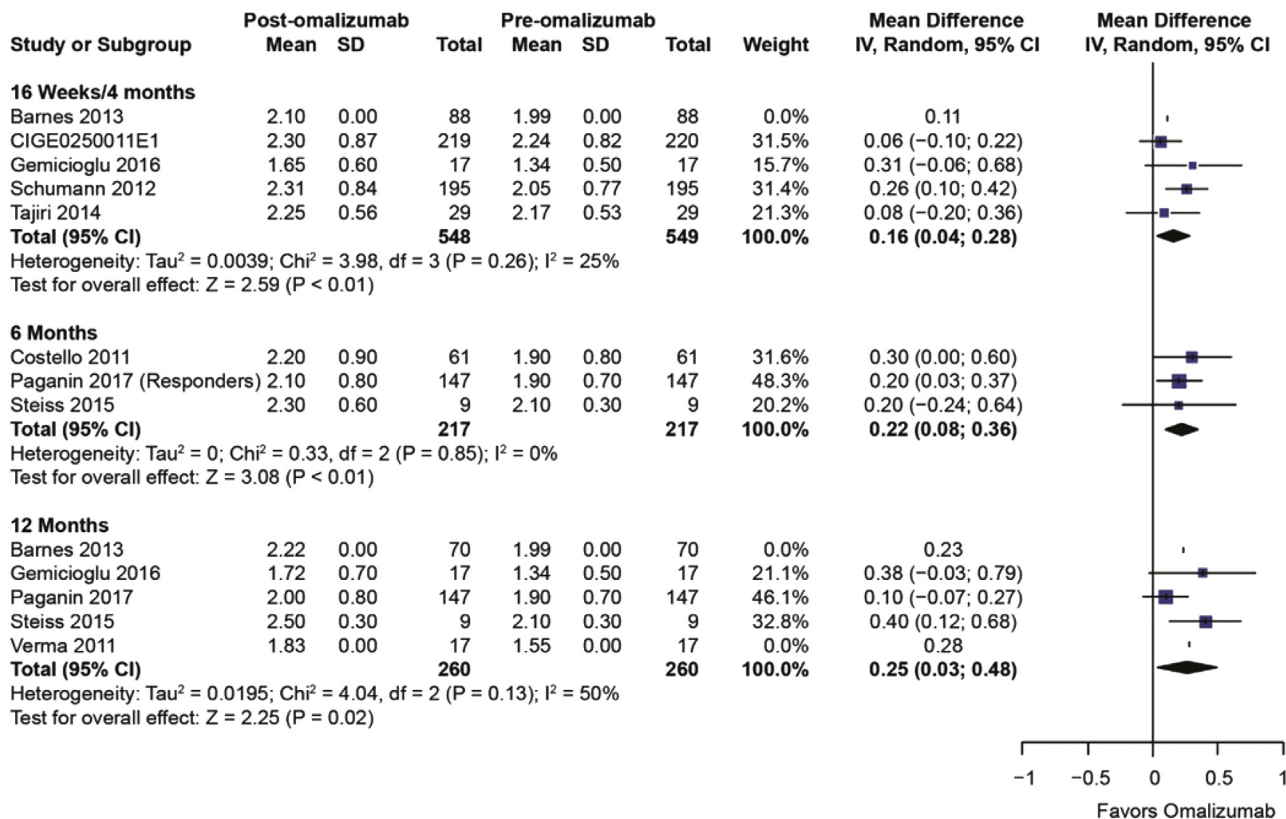
**Hospitalizations.** Hospitalization data were available from 13 publications with a total of 7793 patients at 12 months of omalizumab therapy. The mean number of hospitalizations reduced by 0.52 days (MD [95% CI]: -0.52 [-0.79 to -0.25];  $I^2 = 28%$ ), 1.09 days (MD [95% CI]: -1.09 [-1.59 to -0.60];  $I^2 = 17%$ ), and 0.63 days (MD [95% CI]: -0.63 [-0.85-



**FIGURE 2.** The proportion of GETE responders after 16 weeks, 6 months, and 12 months of omalizumab treatment in the real-world meta-analysis of observational studies. I<sup>2</sup> indicates heterogeneity between the included studies. Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate. CI, Confidence interval; df, degrees of freedom; GETE, global evaluation of treatment effectiveness; IV, inverse variance; MH, Mantel-Haenszel.

to -0.41]; I<sup>2</sup> = 99%) at 16 weeks, 6 months, and 12 months after omalizumab treatment, respectively (P < .01 for all time points; Figure E6, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Likewise, the risk of hospitalization

decreased by 69%, 81%, and 85% after omalizumab treatment for 16 weeks, 6 months, and 12 months, respectively (Figure E6, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).



**FIGURE 3.** Change in FEV<sub>1</sub> after 16 weeks, 6 months, and 12 months of omalizumab treatment in patients with severe allergic asthma. I<sup>2</sup> indicates heterogeneity between the included studies. Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate. CI, Confidence interval; df, degrees of freedom; FEV<sub>1</sub>, forced expiratory volume in 1 second; IV, inverse variance; SD, standard deviation.

**Emergency room visits.** Data on ER visits were available from 11 publications with a total of 6670 patients at 12 months. The mean number of ER visits significantly reduced by 0.76 days after 12 months of omalizumab therapy (MD [95% CI]: -0.76 [-0.94 to -0.58]; P < .01, I<sup>2</sup> = 98%). The risk of ER visits significantly reduced by 54% and 81% after 16 weeks and 6 months of omalizumab therapy, respectively (P < .01 for both time points; Figure E7, available in this article’s Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).

**Unscheduled physician visits.** Data on unscheduled physician visits were available from 11 publications and a total of 5261 patients after 12 months (Figure 8). Treatment with omalizumab for 12 months significantly reduced the number of unscheduled physician visits compared with baseline, with an MD of 2.34 visits (MD [95% CI]: -2.34 [-3.54 to -1.13]; P < .01, I<sup>2</sup> = 98%).

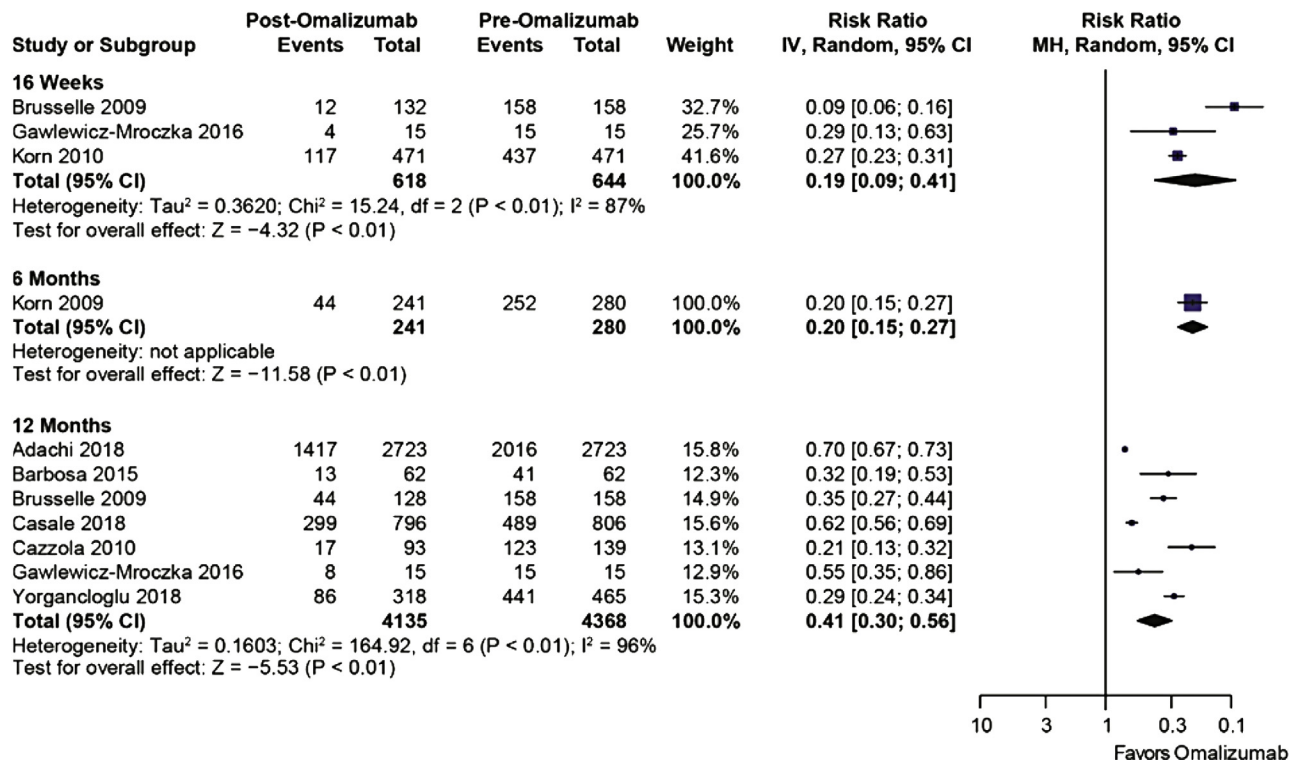
**DISCUSSION**

**Summary of evidence**

This meta-analysis on data from observational/open-label studies showed that omalizumab was associated with an improvement in GETE, lung function (FEV<sub>1</sub>), asthma control, PROs (ACQ, ACT, and AQLQ), and reduction in severe exacerbations, OCS use, HCRU (hospitalizations, ER visits, and

unscheduled physician visits), and school absenteeism across all time points.

This is the first meta-analysis to report investigator GETE ratings from real-world data (RWD) in a large patient pool with over 5900 severe asthmatic patients. We observed that 77% of patients achieved an excellent or good GETE response at week 16 after the start of therapy. The proportion of responders increased after 12 months of therapy, with an average of 82% of patients achieving an excellent or good GETE response. This was in accordance with the results of the EXALT study, in which 72.8% and 76.8% of adolescents and adults patients receiving omalizumab achieved excellent/good responses at weeks 16 and 32,<sup>14</sup> and 91.4% of responder patients at week 16 continued to respond to treatment at week 32.<sup>14</sup> The INNOVATE trial reported that 60.5% of patients treated with omalizumab achieved good/excellent responses, compared with 42.8% in the placebo group at week 28.<sup>4</sup> In the EXTRA study,<sup>15</sup> 65.2%, 68.1%, and 71.1% of patients responded to treatment at weeks 16, 32, and 48, respectively (unpublished data). Further analysis of GETE responders in the RCTs, INNOVATE,<sup>4</sup> EXALT,<sup>14</sup> and EXTRA,<sup>15</sup> with this meta-analysis showed that the proportion of responders was comparable (Figure E8 available in this article’s Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). On average, 65.5% of patients receiving omalizumab showed good or excellent GETE response (95% CI: 53.9%-75.5%) in the pooled analysis of RCTs, with an overdispersion parameter of 2.4



**FIGURE 4.** Omalizumab treatment reduced severe exacerbations in patients with severe allergic asthma. I<sup>2</sup> indicates heterogeneity between the included studies. Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate. CI, Confidence interval; df, degrees of freedom; IV, inverse variance; MH, Mantel-Haenszel.

indicating a slight variability across the trials. The findings from the current meta-analysis and these previously reported RCTs (INNOVATE,<sup>4</sup> EXALT,<sup>14</sup> and EXTRA<sup>15</sup>) show the persistency of response to omalizumab therapy in severe asthmatic population. In this meta-analysis, the effect estimate for GETE remained consistent across all time points, despite the significant heterogeneity between the included studies.

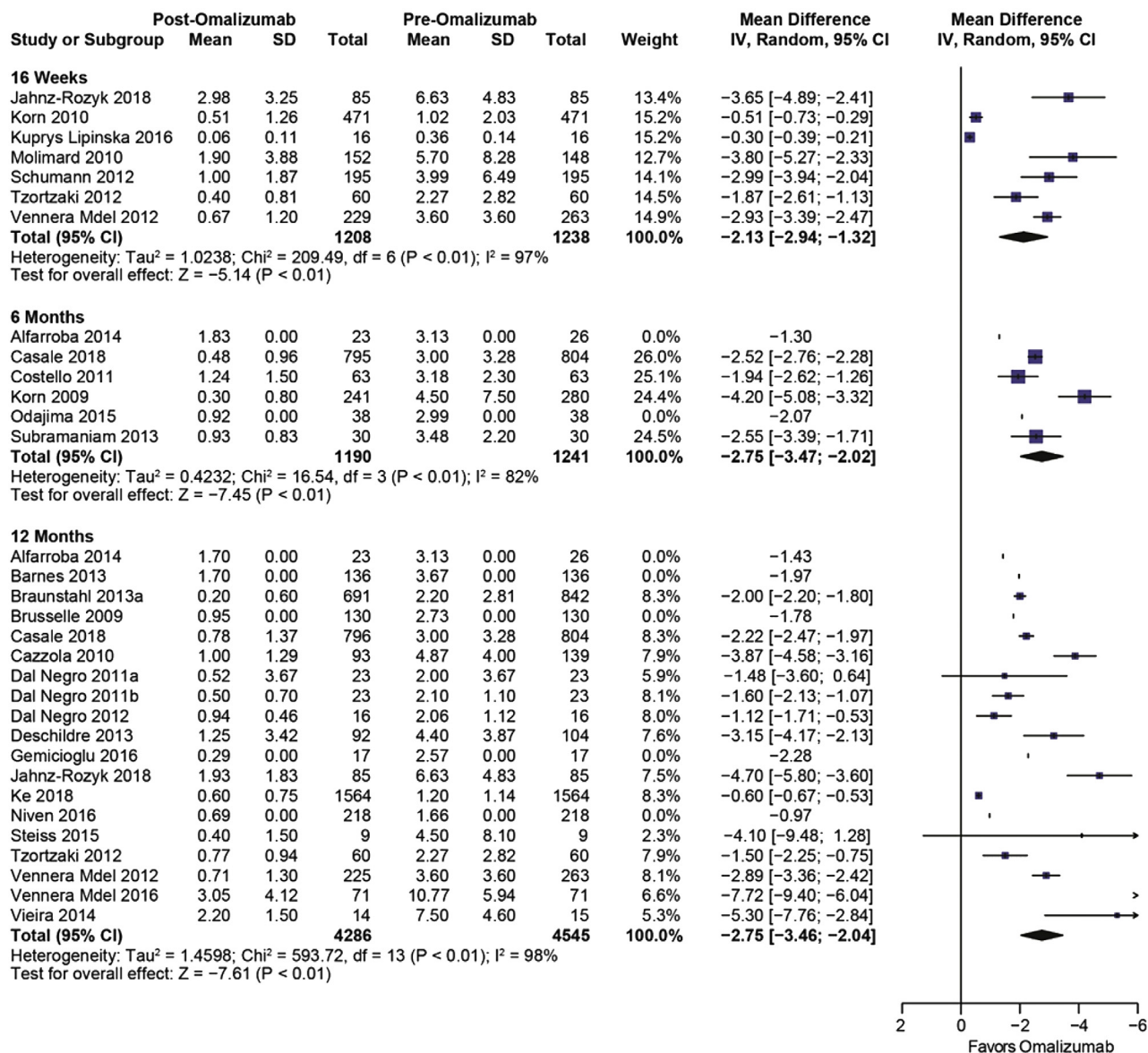
Patients with severe asthma often experience a significant decline in lung function, and the RCTs INNOVATE<sup>4</sup> and EXALT<sup>14</sup> have demonstrated that treatment with omalizumab improves FEV<sub>1</sub> in patients with uncontrolled asthma: 94 mL in the INNOVATE study,<sup>4</sup> and 110 mL at week 16 and 130 mL at week 32 in the EXALT.<sup>14</sup> In the long-term, multicenter, randomized, open-label study (ETOPA), omalizumab added to best standard care therapy (medium- to high-dose inhaled corticosteroid [ICS] with or without long-acting bronchodilator; systemic corticosteroids) resulted in an improvement in morning FEV<sub>1</sub> by an MD of 200 mL, compared with best standard care therapy alone, at the end of study period.<sup>1</sup> The improvement in FEV<sub>1</sub> observed in omalizumab-randomized studies was similar in magnitude to mepolizumab,<sup>101-103</sup> benralizumab,<sup>104,105</sup> reslizumab,<sup>106,107</sup> and dupilumab.<sup>108,109</sup> In this meta-analysis, omalizumab treatment improved FEV<sub>1</sub> by an absolute MD of 160 mL at 16 weeks compared with baseline, and the improvements continued throughout the treatment period with an MD of 220 and 250 mL from baseline at 6 and 12 months, respectively.

Severe asthma is associated with frequent exacerbations that interfere with social and professional life and emotional health of

patients.<sup>110</sup> Several pivotal phase III studies<sup>2,5,111,112</sup> have shown that omalizumab reduced the rate of severe exacerbations. The proportion of patients experiencing an exacerbation significantly decreased after treatment with omalizumab versus placebo during the steroid stable (14.6% vs 23.3%; P = .009) and steroid reduction (21.3% vs 32.3%; P = .004) phases.<sup>2</sup> In another randomized phase III study, patients in the omalizumab group had 58% and 52% fewer exacerbations during the steroid stable phase and steroid reduction phase, respectively, compared with placebo.<sup>5</sup> In a pediatric 52-week RCT, omalizumab reduced the rate of clinically significant asthma exacerbations by 31% and 43% versus placebo, after treatment for 24 and 52 weeks.<sup>111</sup> In another pediatric RCT, omalizumab reduced the proportion of patients experiencing an exacerbation that requires treatment with the double dose of ICS or systemic steroids versus placebo (18.2% vs 38.5%) during the steroid-reduction phase.<sup>112</sup> All phase III studies demonstrated that omalizumab reduced the rate of severe exacerbations compared with placebo similar to other biologics including mepolizumab,<sup>103</sup> reslizumab,<sup>107</sup> benralizumab,<sup>104,113</sup> and dupilumab.<sup>108</sup> This meta-analysis is in line with RCTs as omalizumab reduced the risk of severe exacerbations by approximately 60% after 12 months of treatment compared with baseline. Furthermore, in this study, the proportion of patients receiving OCS decreased by 41% after 12 months of treatment, which is similar to the reductions observed in the RCTs.<sup>114,115</sup>

Severe asthma is also associated with a substantial financial burden due to the direct costs and indirect costs due to loss of work productivity.<sup>116</sup> In RCTs, omalizumab was found to



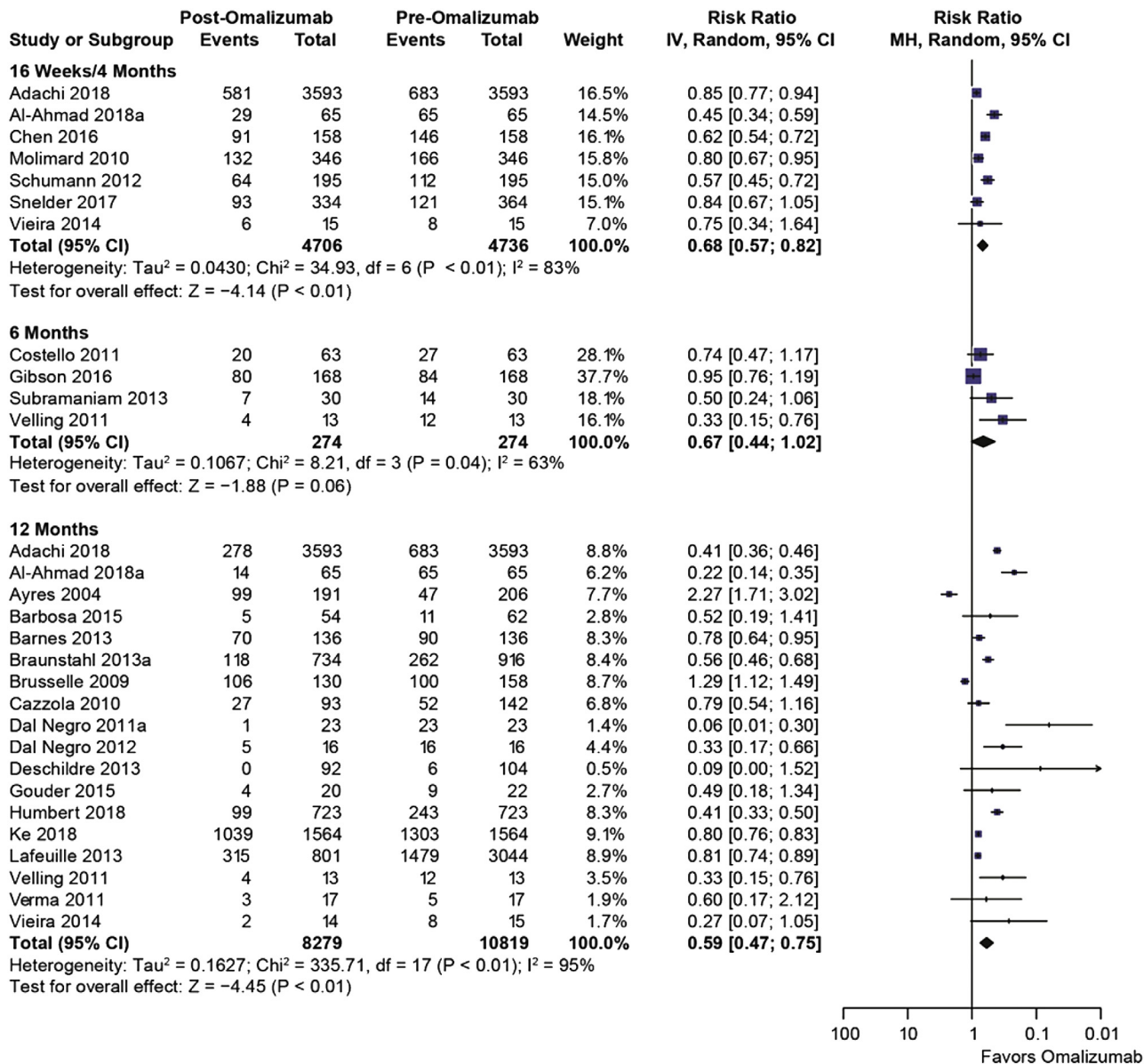


**FIGURE 5.** The mean number of severe exacerbations decreased after treatment with omalizumab in patients with severe allergic asthma. I<sup>2</sup> indicates heterogeneity between the included studies. Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate. CI, Confidence interval; df, degrees of freedom; IV, inverse variance; SD, standard deviation.

reduce the number of days of school absenteeism and unscheduled medical visits in children.<sup>112,117</sup> In the EXALT study, the rates of hospitalizations and ER visits were significantly decreased in patients receiving omalizumab compared with those receiving optimized asthma therapy.<sup>14</sup> Similar results were observed in the ICATA study.<sup>117</sup> In INNOVATE, ER visits for asthma were reduced by 44% in the omalizumab group compared with placebo.<sup>4</sup> Furthermore, the pooled analysis of 3 phase III RCTs<sup>2,5,112</sup> including children and adolescents demonstrated that the rate of unscheduled, asthma-related doctor visits was reduced by 40% in patients treated with omalizumab compared with those treated with placebo.<sup>118</sup> In this study, the mean number of asthma-related unscheduled physician visits significantly reduced after 12 months of treatment, with an MD of

-2.34 (P < .01) visits compared with baseline, whereas only numerical improvement of 2.12 days in the number of missed school or work days was observed.

The PROs including ACQ, ACT, and AQLQ are the validated questionnaires to assess asthma control and health status<sup>119</sup>; and omalizumab has shown to significantly improve asthma control and health-related quality of life in several studies.<sup>3,6,14,15,120</sup> The EXALT study demonstrated a significantly greater reduction in the ACQ score from baseline after omalizumab treatment compared with optimized asthma therapy at weeks 16 and 32.<sup>14</sup> Moreover, omalizumab treatment for 48 weeks improved the proportion of patients achieving the minimal clinically important difference (MCID) of the AQLQ overall score compared with placebo in the EXTRA study.<sup>15</sup> Similar

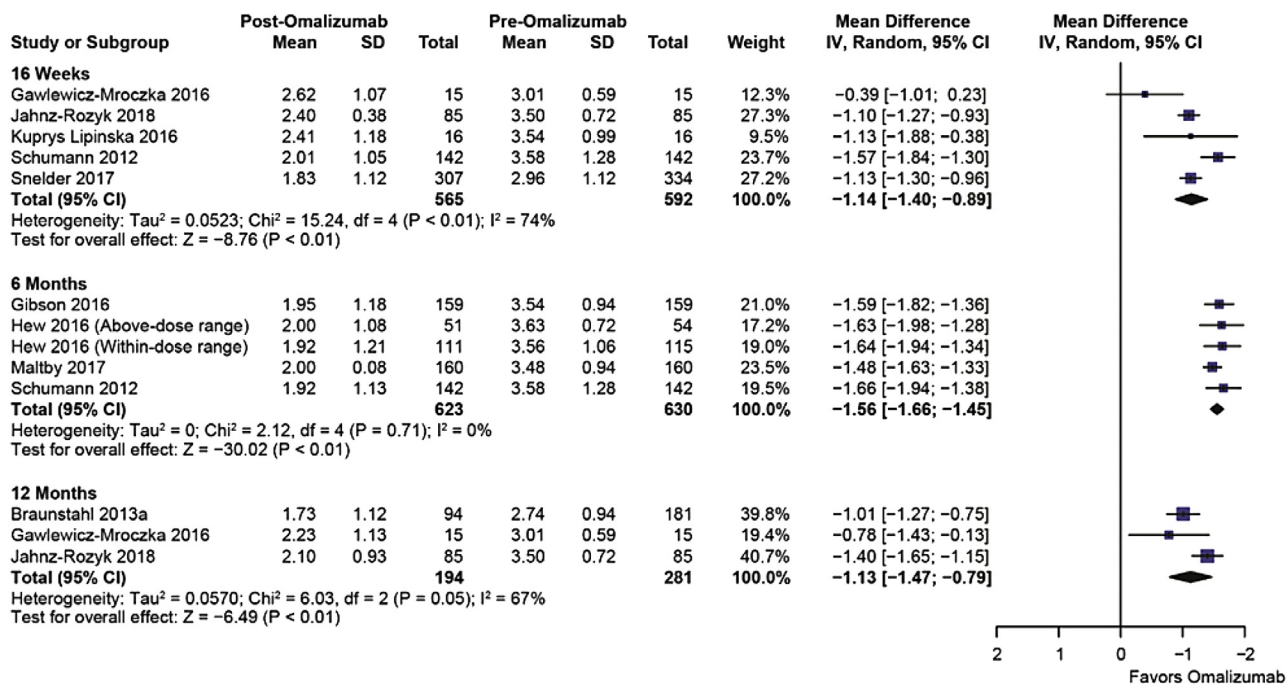


**FIGURE 6.** OCS use reduced after omalizumab treatment in patients with severe allergic asthma. I<sup>2</sup> indicates heterogeneity between the included studies. Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate. *CI*, Confidence interval; *df*, degrees of freedom; *IV*, inverse variance; *OCS*, oral corticosteroid.

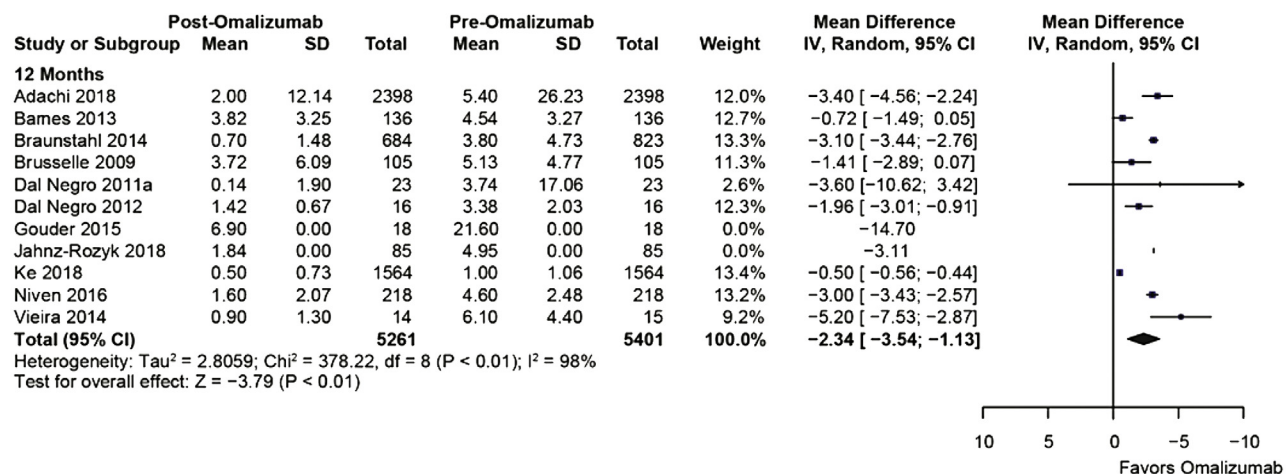
results in terms of the proportion of patients who achieved MCID for the AQLQ score were observed in RCTs (omalizumab vs placebo: 78.8% vs 69.8%; *P* = .050<sup>6</sup> and 58% vs 39%; *P* < .01).<sup>3</sup> In this study, omalizumab treatment significantly decreased the ACQ score and improved the ACT and AQLQ scores starting from 16 weeks with effects maintained until 12 months after therapy, demonstrating the efficacy of omalizumab in improving the PROs in accordance with RCTs. Although safety was not assessed as a part of this meta-analysis, long-term studies have indicated that omalizumab was well tolerated.<sup>19-21</sup>

Use of a random-effects model and analysis of the effect measures as 16 weeks/4 months, and 6 and 12 months to normalize the effect sizes can be considered strengths of this

meta-analysis. The authors also acknowledge few limitations. There was a substantial heterogeneity amongst the studies in terms of the outcomes observed. The risk of bias assessment and quality of individual studies included in the meta-analysis were not evaluated. To limit the bias in analysis, we have considered within-group comparison though the included real-world evidence studies were either phase IV post-marketing surveillance, observational studies with the control group, or uncontrolled studies (before and after). The meta-regression for estimation of dependent effect sizes was out of the scope of analysis and was not performed. However, despite the weakness of the methodologies, the effectiveness results are showing consistent positive results.



**FIGURE 7.** ACQ score decreased after omalizumab treatment in patients with severe allergic asthma. I<sup>2</sup> indicates heterogeneity between the included studies. Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate. ACQ, Asthma Control Questionnaire; CI, confidence interval; df, degrees of freedom; IV, inverse variance.



**FIGURE 8.** Change in the number of unscheduled physician visits after 12 months of omalizumab treatment in patients with severe allergic asthma. I<sup>2</sup> indicates heterogeneity between the included studies. Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate. CI, Confidence interval; df, degrees of freedom; IV, inverse variance; SD, standard deviation.

**CONCLUSIONS**

This meta-analysis of RWD provides consistent evidence on the treatment effectiveness of omalizumab in patients with SAA. It emphasized that the effectiveness of omalizumab did not decrease with time and even demonstrated important changes in full asthma management with 82% achieving GETE asthma control, 250 mL increase in FEV<sub>1</sub>, and 59% reduction in severe

exacerbations after 12 months of treatment. Regardless of the observed heterogeneity between the included studies, we found that add-on omalizumab is also associated with improvement in PROs, and reduced OCS use, hospitalizations, ER, and unscheduled doctor visits. This quantitative synthesis of observational studies confirms, complements, and extends the efficacy findings observed in RCTs in patients with SAA.

## Data sharing

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The trial data availability is according to the criteria and process described on [www.clinicalstudydatarequest.com](http://www.clinicalstudydatarequest.com).

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