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

Jean Bousquet, Marc Humbert, Peter Gibson, Konstantinos Kostikas, Xavier Jaumont, Pascal Pfister, Francis Nissen

Original Article

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

Jean Bousquet, MD, PhD[a,b,c,d], Marc Humbert, MD, PhD[e,f,g], Peter G. Gibson, MBBS, FRACP[h,i], Konstantinos Kostikas, MD, PhD, FCCP[j], Xavier Jaumont, MD[k], Pascal Pfister, MD[k], and Francis Nissen, PhD[k]

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 (≥6 years) treated with omalizumab for ≥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

[a]Contre les Maladies Chroniques pour un VIeillissement Actif (MACVIA) en France European Innovation Partnership on Active and Healthy Ageing Reference Site, Montpellier, France
[b]Centre Hospitalier Universitaire de Montpellier, Montpellier, France
[c]Charité, Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, Berlin, Germany
[d]Department of Dermatology and Allergy, Comprehensive Allergy Center, Berlin Institute of Health, Berlin, Germany
[e]School of Medicine, Université Paris-Saclay, Le Kremlin-Bicêtre, France
[f]INSERM UMR_S 999, Hôpital Marie Lannelongue, Le Plessis-Robinson, France
[g]AP-HP, Department of Respiratory and Intensive Care Medicine, Hôpital Bicêtre, Le Kremlin-Bicêtre, France
[h]Department of Respiratory and Sleep Medicine, John Hunter Hospital, Hunter Medical Research Institute, Newcastle, NSW, Australia
[i]Priority Research Centre for Asthma and Respiratory Disease, the University of Newcastle, Newcastle, NSW, Australia
[j]Respiratory Medicine Department, University of Ioannina Medical School, Ioannina, Greece
[k]Novartis Pharma AG, Basel, Switzerland

This meta-analysis was funded by Novartis Pharma AG, Basel, Switzerland.

Conflicts of interest: J. Bousquet reports personal fees from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Purina, Sanofi-Aventis, Takeda, Teva, and Uriach group; and other from KYomed-Innov. M. Humbert reports personal fees from AstraZeneca, Novartis, Roche, Sanofi, Teva, and GSK, outside the submitted work. P. G. Gibson reports grants and personal fees from Novartis, GSK, AstraZeneca, and Sanofi, outside the submitted work. K. Kostikas was an employee of Novartis Pharma AG at the time of conduct of this study; he has received consulting/lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi, ELPEN, GSK, Menarini, Novartis, and Sanofi. X. Jaumont and P. Pfister are employees of Novartis Pharma AG, Basel, Switzerland. F. Nissen reports grants from Novartis Pharma AG during the conduct of the meta-analysis; consulted for Hoffmann-La Roche; and reports grants from GSK, outside the submitted work.

Received for publication March 1, 2020; revised December 22, 2020; accepted for publication January 6, 2021.

Available online January 21, 2021.

Corresponding author: Jean Bousquet, MD, PhD, Centre Hospitalier Universitaire de Montpellier, 191 Av. du Doyen Gaston Giraud, 34295 Montpellier, France. E-mail: jean.bousquet@orange.fr.

2213-2198

https://doi.org/10.1016/j.jaip.2021.01.011

Abbreviations used
ACQ- Asthma Control Questionnaire
ACT- Asthma Control Test
AQLQ- Asthma Quality of Life Questionnaire
CI- Confidence interval
ER- Emergency room
FEV_1- 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. **(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,[1-6] 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.[7] Furthermore, medication adherence, the key pillar for treatment effectiveness, is closely monitored in RCTs, which is not always the case in real-world settings.[7] 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[8] 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.[8] A meta-analysis conducted on these noncontrolled studies demonstrated the real-life pharmacotherapeutic effectiveness of omalizumab and complemented the efficacy data from RCTs.[9] 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.[10] However, to date, no meta-analysis has summarized the real-world effectiveness of omalizumab in patients ≥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 ≥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, the Novartis clinical trials database (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 ≥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.[11]

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). The secondary outcomes reported were the mean change in forced expiratory volume in 1 second (FEV_1), 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^2 statistics with upper limits of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively.[12] Studies were weighted using the DerSimonian and Laird random-effects model.[13]

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,[14] EXTRA,[15] and INNOVATE[4]). 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).[16]

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.[1,14,17-100] Eighty-four studies were identified from the literature databases, and 2 unpublished studies were identified from the 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). 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 (≥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; $P < .01$, $I^2 = 96\%$), 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 ($I^2 = 97\%$; Figure 2). Despite this heterogeneity, the GETE responses were consistently positive (Figure 2).

Forced expiratory volume in 1 second

Data on FEV_1 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_1 with mean change from baseline of 160 mL at 16 weeks (95% CI: 0.04-0.28; $P < .01$, $I^2 = 25\%$), 220 mL at 6 months (95% CI: 0.08-0.36; $P < .01$, $I^2 = 0\%$), and 250 mL at 12 months (95% CI: 0.03-0.48; $P = .02$, $I^2 = 50\%$) 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]; $P < .01$, $I^2 = 87\%$) and 59% (RR [95% CI]: 0.41 [0.30-0.56]; $P < .01$, $I^2 = 96\%$) 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]; $P < .01$, $I^2 = 97\%$), 2.75 (MD [95% CI]: −2.75 [−3.74 to −2.02]; $P < .01$, $I^2 = 82\%$), and 2.75 (MD [95% CI]: −2.75 [−3.46 to −2.04]; $P < .01$, $I^2 = 98\%$) 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

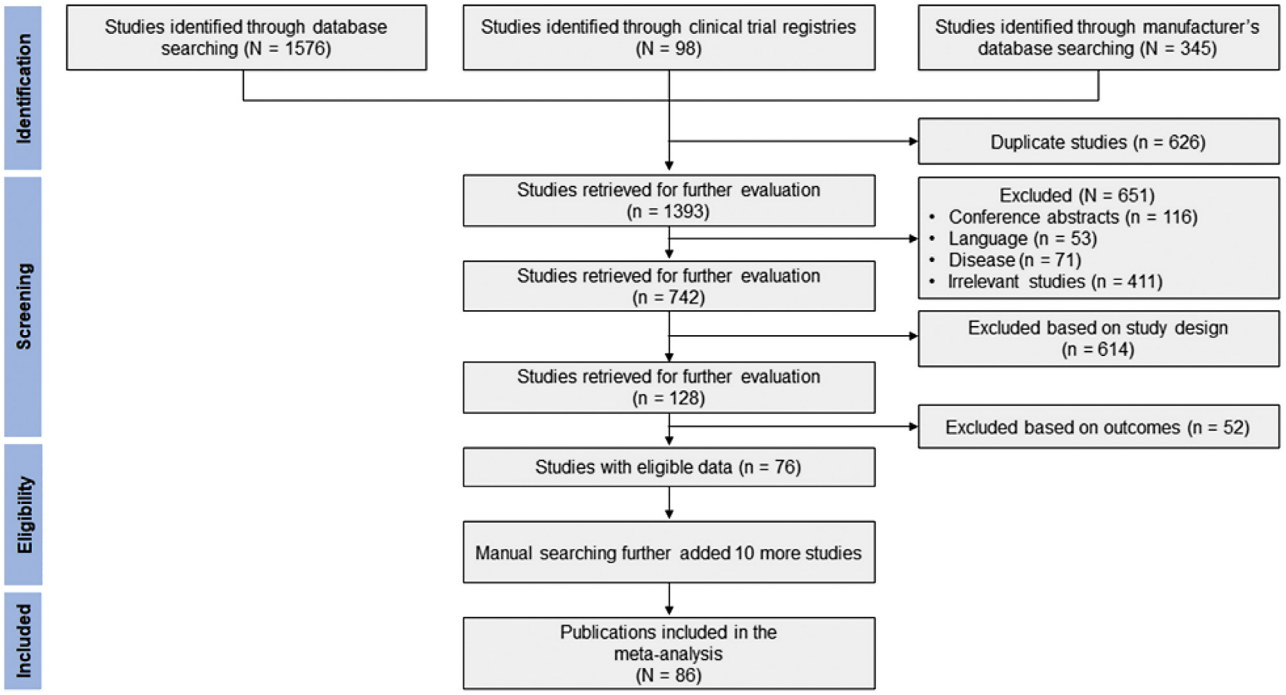

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis flow diagram. The core and extension studies by Odajima et al were considered as 2 separate publications bringing the total number of publications to 86.

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 ≥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). 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).

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).

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). 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). 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

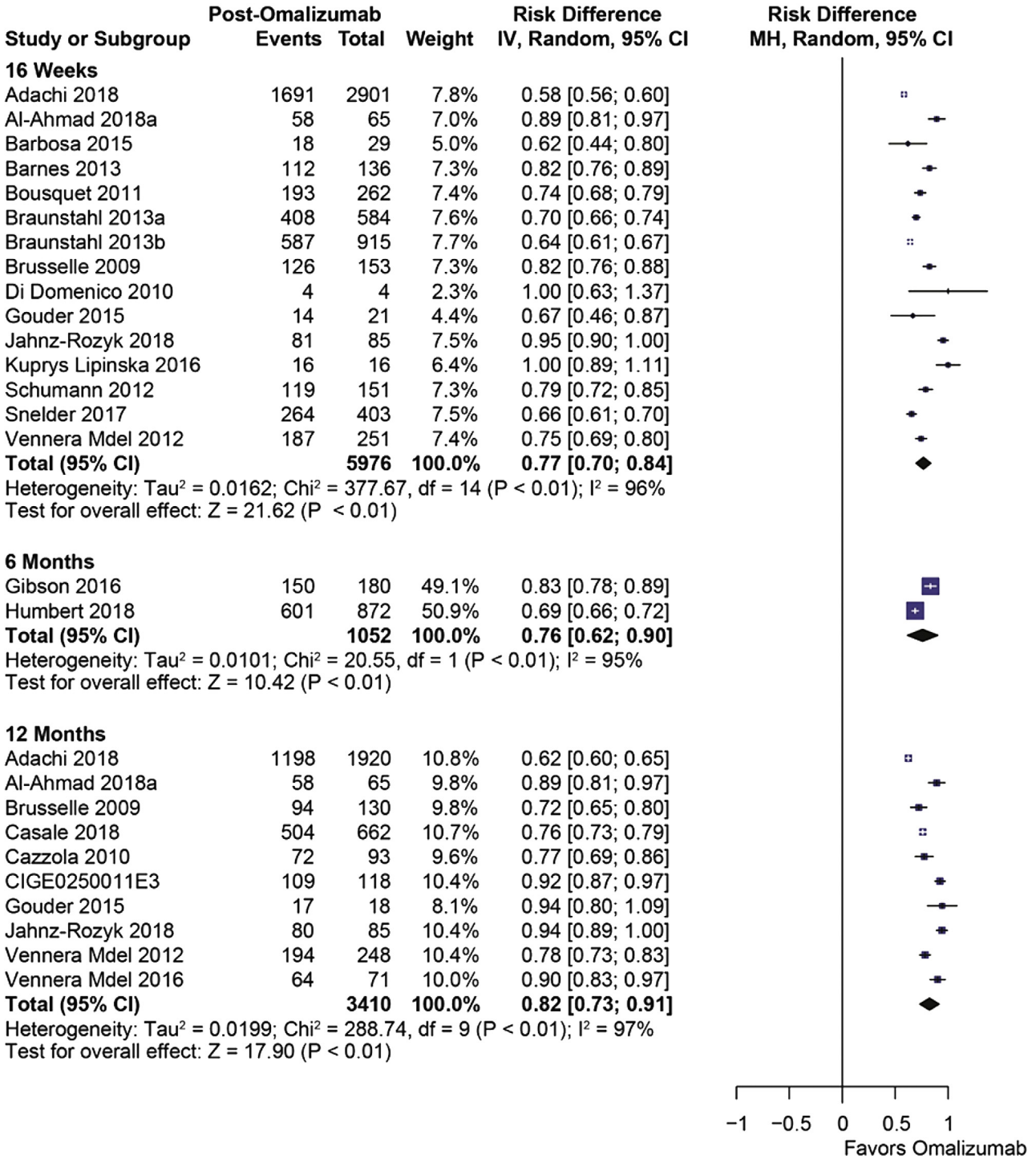

FIGURE 2. The proportion of GETE responders after 16 weeks, 6 months, and 12 months of omalizumab treatment in the real-world meta-analysis of observational studies. I^2 indicates heterogeneity between the included studies. Squares indicate the study-specific estimate (the size of the square reflects 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]; $I^2 = 99\%$) 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). 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).

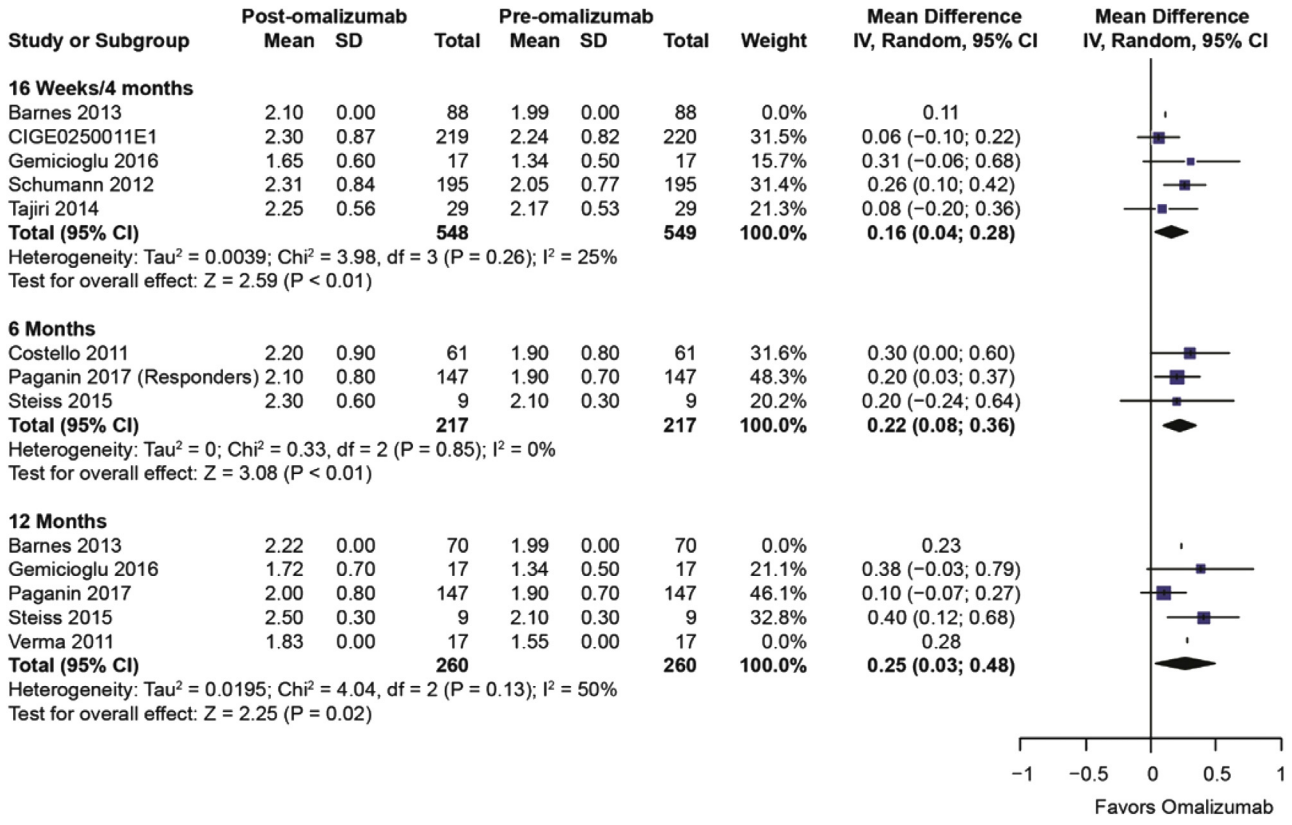

FIGURE 3. Change in FEV_1 after 16 weeks, 6 months, and 12 months of omalizumab treatment in patients with severe allergic asthma. I^2 indicates heterogeneity between the included studies. Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 95% CI; diamonds indicate the pooled estimate. *CI*, Confidence interval; *df*, degrees of freedom; *FEV_1*, 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]; $P < .01$, $I^2 = 98\%$). 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).

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]; $P < .01$, $I^2 = 98\%$).

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_1), 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,[14] and 91.4% of responder patients at week 16 continued to respond to treatment at week 32.[14] 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.[4] In the EXTRA study,[15] 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,[4] EXALT,[14] and EXTRA,[15] 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). 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

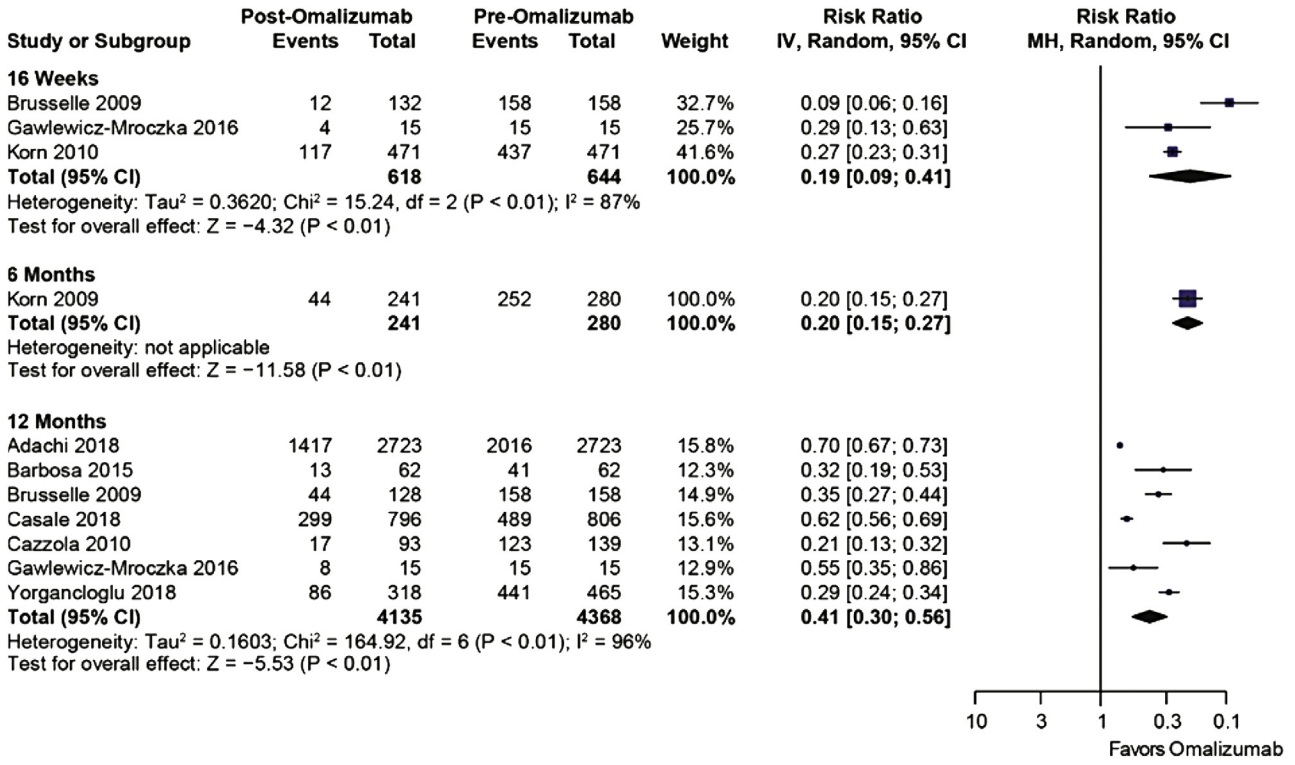

FIGURE 4. Omalizumab treatment reduced severe exacerbations in patients with severe allergic asthma. I^2 indicates heterogeneity between the included studies. Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate 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,[4] EXALT,[14] and EXTRA[15]) 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[4] and EXALT[14] have demonstrated that treatment with omalizumab improves FEV_1 in patients with uncontrolled asthma: 94 mL in the INNOVATE study,[4] and 110 mL at week 16 and 130 mL at week 32 in the EXALT.[14] 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_1 by an MD of 200 mL, compared with best standard care therapy alone, at the end of study period.[1] The improvement in FEV_1 observed in omalizumab-randomized studies was similar in magnitude to mepolizumab,[101-103] benralizumab,[104,105] reslizumab,[106,107] and dupilumab.[108,109] In this meta-analysis, omalizumab treatment improved FEV_1 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.[110] Several pivotal phase III studies[2,5,111,112] 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.[2] 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.[5] 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.[111] 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.[112] All phase III studies demonstrated that omalizumab reduced the rate of severe exacerbations compared with placebo similar to other biologics including mepolizumab,[103] reslizumab,[107] benralizumab,[104,113] and dupilumab.[108] 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.[114,115]

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

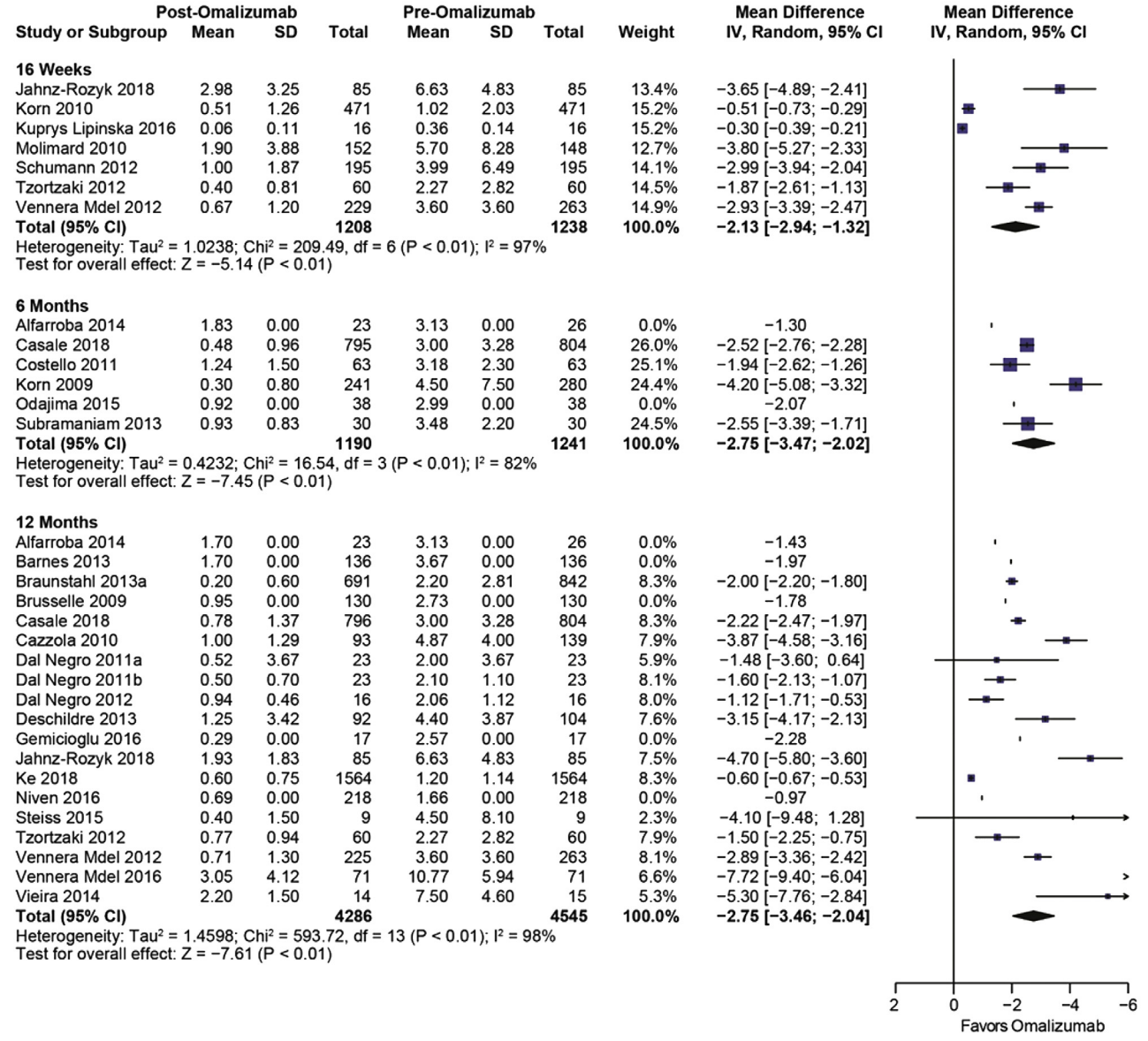

FIGURE 5. The mean number of severe exacerbations decreased after treatment with omalizumab in patients with severe allergic asthma. I^2 indicates heterogeneity between the included studies. Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the 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.[112,117] 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.[14] Similar results were observed in the ICATA study.[117] In INNOVATE, ER visits for asthma were reduced by 44% in the omalizumab group compared with placebo.[4] Furthermore, the pooled analysis of 3 phase III RCTs[2,5,112] 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.[118] 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[119]; and omalizumab has shown to significantly improve asthma control and health-related quality of life in several studies.[3,6,14,15,120] 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.[14] 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.[15] Similar

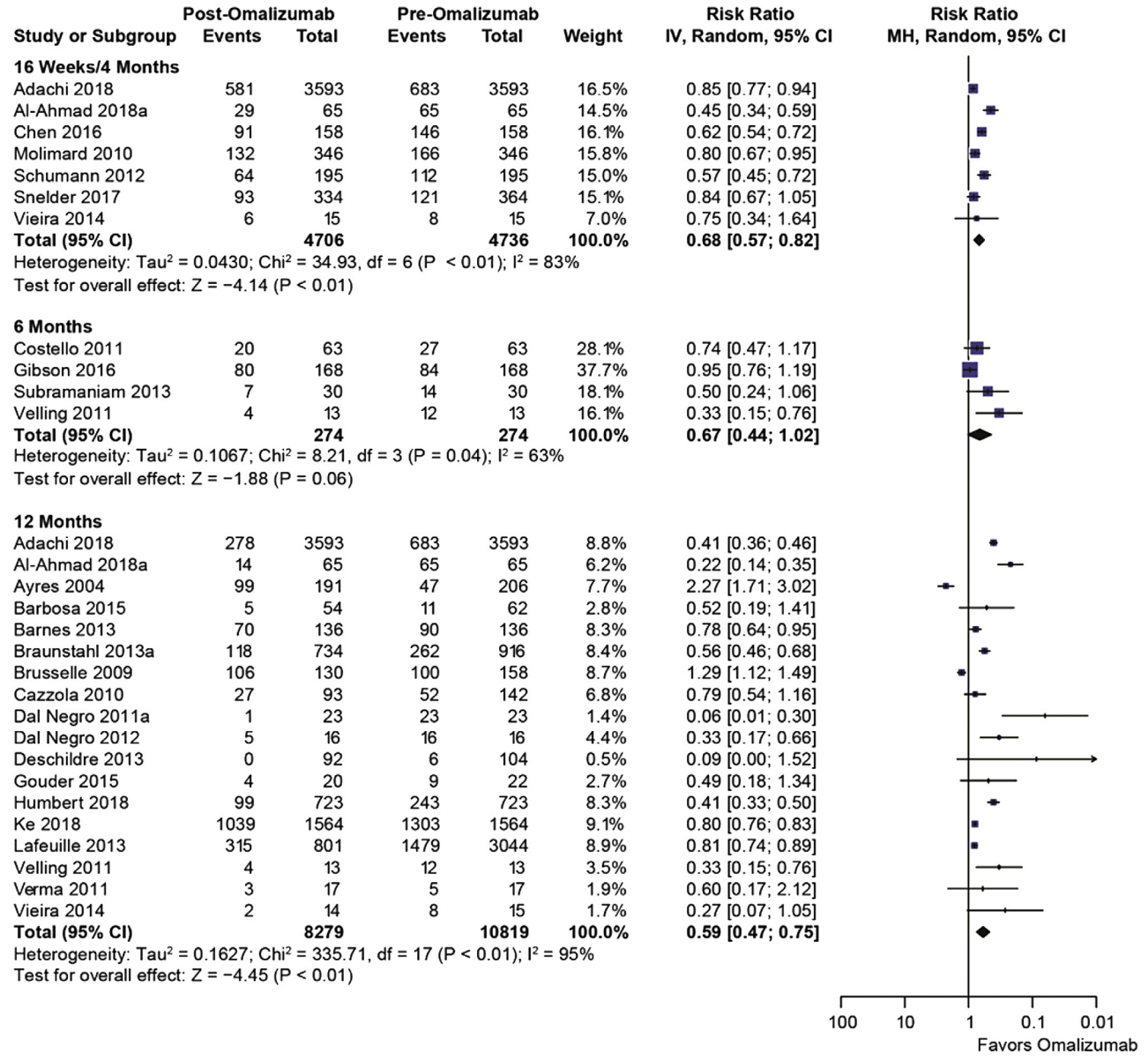

FIGURE 6. OCS use reduced after omalizumab treatment in patients with severe allergic asthma. I^2 indicates heterogeneity between the included studies. Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate the 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%; $P = .050$[6] and 58% vs 39%; $P < .01$).[3] 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.[19-21]

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.

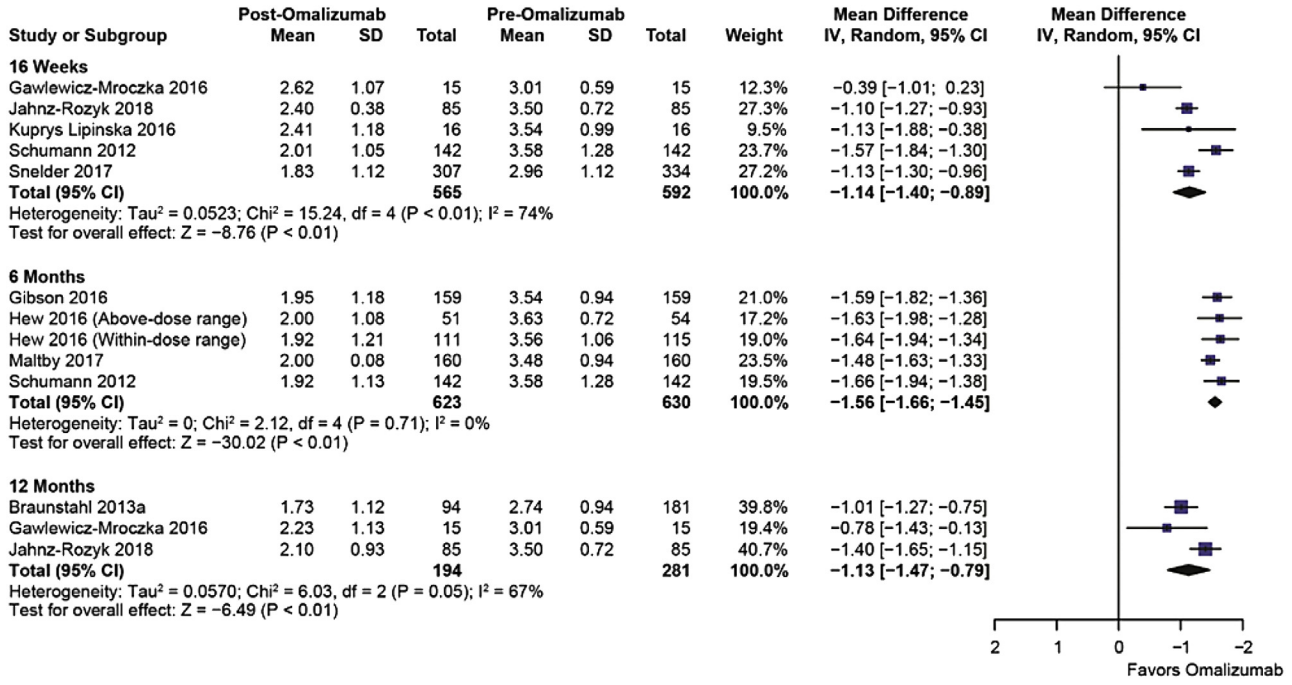

FIGURE 7. ACQ score decreased after omalizumab treatment in patients with severe allergic asthma. I^2 indicates heterogeneity between the included studies. Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight in the analysis); horizontal lines indicate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

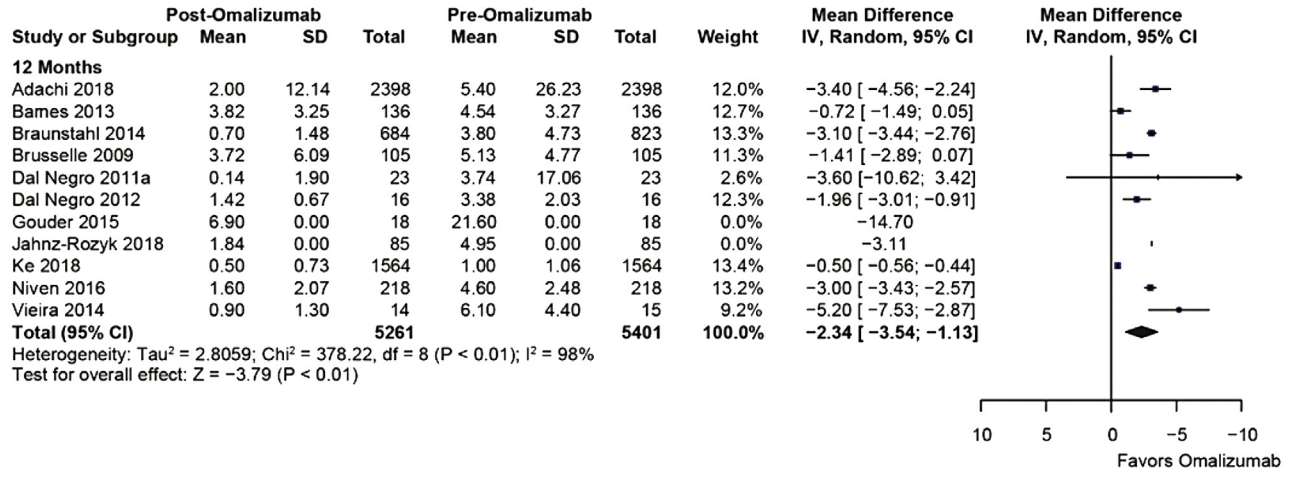

FIGURE 8. Change in the number of unscheduled physician visits after 12 months of omalizumab treatment in patients with severe allergic asthma. I^2 indicates heterogeneity between the included studies. Squares indicate the study-specific estimate (the size of the square reflects the study-specific weight 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_1, 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.

Acknowledgments

The authors thank Vatsal Vithlani, Lakshmi Narendra Bodduluru, and A. S. Shaik (Novartis) for providing medical writing/editorial support, in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

REFERENCES

1. Ayres JG, Higgins B, Chilvers ER, Ayre G, Blogg M, Fox H. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. Allergy 2004;59:701-8.
2. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol 2001;108:184-90.
3. Holgate ST, Chuchalin AG, Hebert J, Lotvall J, Persson GB, Chung KF, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. Clin Exp Allergy 2004;34:632-8.
4. Humbert M, Beasley R, Ayres J, Slavin R, Hebert 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.
5. Soler 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.
6. Vignola AM, Humbert M, Bousquet J, Boulet LP, Hedgecock S, Blogg M, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. Allergy 2004;59:709-17.
7. Price D, Brusselle G, Roche N, Freeman D, Chisholm A. Real-world research and its importance in respiratory medicine. Breathe (Sheff) 2015;11:26-38.
8. 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.
9. Alhossan A, Lee CS, MacDonald K, Abraham I. "Real-life" effectiveness studies of omalizumab in adult patients with severe allergic asthma: meta-analysis. J Allergy Clin Immunol Pract 2017;5:1362-1370.e2.
10. MacDonald KM, Kavati A, Ortiz B, Alhossan A, Lee CS, Abraham I. Short- and long-term real-world effectiveness of omalizumab in severe allergic asthma: systematic review of 42 studies published 2008-2018. Expert Rev Clin Immunol 2019;15:553-69.
11. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
12. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
13. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials 2015;45:139-45.
14. 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.
15. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. Ann Intern Med 2011;154:573-82.
16. The R Foundation for Statistical Computing Version 3.4.1. Available from: https://www.r-project.org/. Accessed February 2, 2020.
17. CIGE0250011E1. An open-label extension to assess long-term safety and tolerability of omalizumab treatment in adolescents and adults with severe allergic asthma who participated in the 32-week core study. Available from: www.novctrd.com. Accessed December 15, 2020.
18. CIGE0250011E3. An open-label extension study to assess long term safety and tolerability of omalizumab treatment in adults and adolescents with severe allergic asthma who participated in the 52 week CIGE025 0011E2 study. Available from: www.novctrd.com. Accessed December 15, 2020.
19. Adachi M, Kozawa M, Yoshisue H, Lee Milligan K, Nagasaki M, Sasajima T, et al. Real-world safety and efficacy of omalizumab in patients with severe allergic asthma: a long-term post-marketing study in Japan. Respir Med 2018;141:56-63.
20. Al-Ahmad M, Arifhodzic N, Nurkic J, Maher A, Rodriguez-Bouza T, Al-Ahmed N, et al. "Real-life" efficacy and safety aspects of 4-year omalizumab treatment for asthma. Med Princ Pract 2018;27:260-6.
21. Al-Ahmad M, Nurkic J, Maher A, Arifhodzic N, Jusufovic E. Tolerability of omalizumab in asthma as a major compliance factor: 10-year follow up. Open Access Maced J Med Sci 2018;6:1839-44.
22. Alfarroba S, Videira W, Galvao-Lucas C, Carvalho F, Barbara C. Clinical experience with omalizumab in a Portuguese severe asthma unit. Rev Port Pneumol 2014;20:78-83.
23. Ancochea J, Chivato T, Casan P, Picado C, Herraez L, Casafont J. Profile of patients treated with omalizumab in routine clinical practice in Spain. Allergol Immunopathol (Madr) 2014;42:102-8.
24. 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.
25. Braunstahl GJ, Canvin J, Peachey G, Chen CW, Georgiou P. Healthcare resource utilization in patients receiving omalizumab for allergic asthma in a real-world setting. Biol Ther 2014;4:57-67.
26. Braunstahl GJ, Chen CW, Maykut R, Georgiou P, Peachey G, Bruce J. The eXpeRience registry: the 'real-world' effectiveness of omalizumab in allergic asthma. Respir Med 2013;107:1141-51.
27. Braunstahl GJ, Chlumsky 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.
28. 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.
29. Caminati M, Senna G, Chieco Bianchi F, Marchi MR, Vianello A, Micheletto C, et al. Omalizumab management beyond clinical trials: the added value of a network model. Pulm Pharmacol Ther 2014;29:74-9.
30. Casale TB, Luskin AT, Busse W, Zeiger RS, Trzaskoma B, Yang M, et al. Omalizumab effectiveness by biomarker status in patients with asthma: evidence from PROSPERO, a prospective real-world study. J Allergy Clin Immunol Pract 2019;7:156-164.e1.
31. 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.
32. Chen HC, Huang CD, Chang E, Kuo HP. Efficacy of omalizumab (Xolair(R)) in patients with moderate to severe predominately chronic oral steroid dependent asthma in Taiwan: a retrospective, population-based database cohort study. BMC Pulm Med 2016;16:3.
33. 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.
34. Dal Negro RW, Guerriero M, Micheletto C, Tognella S, Visconti M. Changes in total IgE plasma concentration measured at the third month during anti-IgE treatment predict future exacerbation rates in difficult-to-treat atopic asthma: a pilot study. J Asthma 2011;48:437-41.
35. Dal Negro RW, Pradelli L, Tognella S, Micheletto C, Iannazzo S. Cost-utility of add-on omalizumab in difficult-to-treat allergic asthma in Italy. Eur Ann Allergy Clin Immunol 2011;43:45-53.
36. Dal Negro RW, Tognella S, Pradelli L. A 36-month study on the cost/utility of add-on omalizumab in persistent difficult-to-treat atopic asthma in Italy. J Asthma 2012;49:843-8.
37. Deschildre A, Marguet C, Salleron J, Pin I, Rittie JL, Derelle J, et al. Add-on omalizumab in children with severe allergic asthma: a 1-year real life survey. Eur Respir J 2013;42:1224-33.
38. Di Domenico M, Polverino M, De Rosa C, Ricci V, Bisogno A, Capasso A. Xolair: a new monoclonal drug anti-IgE antibody for the treatment of allergic asthma. Biomed Res 2011;22:111-9.

39. Eisner MD, Zazzali JL, Miller MK, Bradley MS, Schatz M. Longitudinal changes in asthma control with omalizumab: 2-year interim data from the EXCELS Study. J Asthma 2012;49:642-8.
40. Gawlewicz-Mroczka A, Zastrzeżyńska W, Przybyszowski M, Ćmiel A, Sładek K. Effectiveness of omalizumab therapy in patients with highly severe allergic asthma treated in Department of Pulmonology in Krakow. Alergologia Polska Pol J Allergol 2016;3:127-33.
41. Gemicioglu B, Caliskaner Ozturk B, Duman B. Comparison of allergic asthma patients treated with omalizumab and non-allergic patients treated with continuous oral corticosteroids: results of five year follow-up therapies. Tuberk Toraks 2016;64:97-104.
42. Gibson PG, Reddel H, McDonald VM, Marks G, Jenkins C, Gillman A, et al. Effectiveness and response predictors of omalizumab in a severe allergic asthma population with a high prevalence of comorbidities: the Australian Xolair Registry. Intern Med J 2016;46:1054-62.
43. Gibson PG, Taramarcaz P, McDonald VM. Use of omalizumab in a severe asthma clinic. Respirology 2007;12(Suppl 3):S35-44. discussion: S5-7.
44. Gouder C, West LM, Montefort S. The real-life clinical effects of 52 weeks of omalizumab therapy for severe persistent allergic asthma. Int J Clin Pharm 2015;37:36-43.
45. 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.
46. Hew M, Gillman A, Sutherland M, Wark P, Bowden J, Guo M, et al. Real-life effectiveness of omalizumab in severe allergic asthma above the recommended dosing range criteria. Clin Exp Allergy 2016;46:1407-15.
47. Huang YC, Weng CM, Lee MJ, Lin SM, Wang CH, Kuo HP. Endotypes of severe allergic asthma patients who clinically benefit from anti-IgE therapy. Clin Exp Allergy 2019;49:44-53.
48. Humbert M, Taille C, Mala L, Le Gros V, Just J, Molimard M. Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study. Eur Respir J 2018;51:1702523.
49. Jahnz-Rozyk K, Lis J, Warchol M, Kucharczyk A. Clinical and economic impact of a one-year treatment with omalizumab in patients with severe allergic asthma within a drug programme in Poland. BMC Pulm Med 2018; 18:48.
50. Ke X, Kavati A, Wertz D, Huang Q, Wang L, Willey VJ, et al. Real-world clinical characteristics, treatment patterns, and exacerbations in US patients with asthma newly treated with omalizumab. Clin Ther 2018;40:1140-1158.e4.
51. Kelmenson DA, Kelly VJ, Winkler T, Kone MT, Musch G, Melo MF, 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.
52. 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.
53. 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.
54. Kuprys-Lipinska I, Majak P, Molinska J, Kuna P. Effectiveness of the Polish program for the treatment of severe allergic asthma with omalizumab: a single-center experience. BMC Pulm Med 2016;16:61.
55. Lafeuille MH, Dean J, Zhang J, Duh MS, Gorsh B, Lefebvre P. Impact of omalizumab on emergency-department visits, hospitalizations, and corticosteroid use among patients with uncontrolled asthma. Ann Allergy Asthma Immunol 2012;109:59-64.
56. Lafeuille MH, Gravel J, Zhang J, Gorsh B, Figliomeni M, Lefebvre P. Association between consistent omalizumab treatment and asthma control. J Allergy Clin Immunol Pract 2013;1:51-7.
57. Lee JH, Lee HY, Jung CG, Ban GY, Shin YS, Ye YM, et al. Therapeutic effect of omalizumab in severe asthma: a real-world study in Korea. Allergy Asthma Immunol Res 2018;10:121-30.
58. Levy AN, Garcia ARAJ, Garcia-Agua Soler N, Sanjuan MV. Cost-effectiveness of omalizumab in severe persistent asthma in Spain: a real-life perspective. J Asthma 2015;52:205-10.
59. Lopez Tiro JJ, Contreras EA, del Pozo ME, Gomez Vera J, Larenas Linnemann D. Real life study of three years omalizumab in patients with difficult-to-control asthma. Allergol Immunopathol (Madr) 2015;43:120-6.
60. Maltby S, Gibson PG, Powell H, McDonald VM. Omalizumab treatment response in a population with severe allergic asthma and overlapping COPD. Chest 2017;151:78-89.
61. Mansur AH, Srivastava S, Mitchell V, Sullivan J, Kasujee I. Longterm clinical outcomes of omalizumab therapy in severe allergic asthma: study of efficacy and safety. Respir Med 2017;124:36-43.
62. Menzella F, Facciolongo N, Piro R, Formisano D, Roggeri A, Simonazzi A, et al. Clinical and pharmacoeconomic aspects of omalizumab: a 4-year follow-up. Ther Adv Respir Dis 2012;6:87-95.
63. Menzella F, Galeone C, Formisano D, Castagnetti C, Ruggiero P, Simonazzi A, et al. Real-life efficacy of omalizumab after 9 years of follow-up. Allergy Asthma Immunol Res 2017;9:368-72.
64. 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.
65. 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.
66. Niven RM, Saralaya D, Chaudhuri R, Masoli M, Clifton I, Mansur AH, et al. Impact of omalizumab on treatment of severe allergic asthma in UK clinical practice: a UK multicentre observational study (the APEX II study). BMJ Open 2016;6:e011857.
67. 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.
68. Odajima H, Ebisawa M, Nagakura T, Fujisawa T, Akasawa A, Ito K, et al. Omalizumab in Japanese children with severe allergic asthma uncontrolled with standard therapy. Allergol Int 2015;64:364-70.
69. Odajima H, Ebisawa M, Nagakura T, Fujisawa T, Akasawa A, Ito K, et al. Long-term safety, efficacy, pharmacokinetics and pharmacodynamics of omalizumab in children with severe uncontrolled asthma. Allergol Int 2017;66: 106-15.
70. Oliveira M, Vieira M, Coutinho D, Ladeira I, Pascoal I, Ferreira J, et al. Severe asthma in obese patients: improvement of lung function after treatment with omalizumab. Pulmonology 2019;25:15-20.
71. Ozgur ES, Ozge C, Ilvan A, Nayci SA. Assessment of long-term omalizumab treatment in patients with severe allergic asthma long-term omalizumab treatment in severe asthma. J Asthma 2013;50:687-94.
72. Pace E, Ferraro M, Bruno A, Chiappara G, Bousquet J, Gjomarkaj M. Clinical benefits of 7 years of treatment with omalizumab in severe uncontrolled asthmatics. J Asthma 2011;48:387-92.
73. Paganin F, Mangiapan G, Proust A, Prudhomme A, Attia J, Marchand-Adam S, et al. Lung function parameters in omalizumab responder patients: an interesting tool? Allergy 2017;72:1953-61.
74. Pelaia G, Gallelli L, Romeo P, Renda T, Busceti MT, Proietto A, et al. Omalizumab decreases exacerbation frequency, oral intake of corticosteroids and peripheral blood eosinophils in atopic patients with uncontrolled asthma. Int J Clin Pharmacol Ther 2011;49:713-21.
75. Pereira Barbosa M, Bugalho de Almeida A, Pereira C, Chen CW, Georgiou P, Peachey G. Real-life efficacy and safety of omalizumab in Portuguese patients with persistent uncontrolled asthma. Rev Port Pneumol (2006) 2015;21:151-6.
76. Rottem M. Omalizumab reduces corticosteroid use in patients with severe allergic asthma: real-life experience in Israel. J Asthma 2012;49:78-82.
77. Rubin AS, 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.
78. Saji J, Yamamoto T, Arai M, Mineshita M, Miyazawa T. Efficacy of long-term omalizumab therapy in patients with severe asthma. Respir Investig 2017;55: 114-20.
79. Schumann C, Kropf C, Wibmer T, Rudiger S, Stoiber KM, Thielen A, et al. Omalizumab in patients with severe asthma: the XCLUSIVE study. Clin Respir J 2012;6:215-27.
80. Siergiejko Z, Swiebocka E, Smith N, Peckitt C, Leo J, Peachey G, et al. Oral corticosteroid sparing with omalizumab in severe allergic (IgE-mediated) asthma patients. Curr Med Res Opin 2011;27:2223-8.
81. Snelder SM, Weersink EJM, Braunstahl GJ. 4-month omalizumab efficacy outcomes for severe allergic asthma: the Dutch National Omalizumab in Asthma Registry. Allergy Asthma Clin Immunol 2017;13:34.
82. Sousa AS, Pereira AM, Fonseca JA, Azevedo LF, Abreu C, Arrobas A, et al. Asthma control and exacerbations in patients with severe asthma treated with omalizumab in Portugal. Rev Port Pneumol 2015;21: 327-33.
83. Sposato B, Scalese M, Latorre M, Scichilone N, Matucci A, Milanese M, et al. Effects of omalizumab in severe asthmatics across ages: a real life Italian experience. Respir Med 2016;119:141-9.
84. Steiss JO, Schmidt A, Rudloff S. Monitoring of omalizumab therapy by measuring free IgE using a bedside immunoassay. Clin Lab 2015;61:31-7.

85. Storms W, Bowdish MS, Farrar JR. Omalizumab and asthma control in patients with moderate-to-severe allergic asthma: a 6-year pragmatic data review. Allergy Asthma Proc 2012;33:172-7.
86. 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 centre for asthma in Ireland. QJM 2013;106:631-4.
87. 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.
88. Tajiri T, Matsumoto H, Gon Y, Ito R, Hashimoto S, Izuhara K, et al. Utility of serum periostin and free IgE levels in evaluating responsiveness to omalizumab in patients with severe asthma. Allergy 2016;71:1472-9.
89. 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;113:470-475.e2.
90. Tat TS, Cilli A. Evaluation of long-term safety and efficacy of omalizumab in elderly patients with uncontrolled allergic asthma. Ann Allergy Asthma Immunol 2016;117:546-9.
91. 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.
92. Velling P, Skowasch D, Pabst S, Jansen E, Tuleta I, Grohe C. Improvement of quality of life in patients with concomitant allergic asthma and atopic dermatitis: one year follow-up of omalizumab therapy. Eur J Med Res 2011;16:407-10.
93. Vennera Mdel C, Perez De Llano L, Bardagi S, Ausin P, Sanjuas C, Gonzalez H, et al. Omalizumab therapy in severe asthma: experience from the Spanish registry—some new approaches. J Asthma 2012;49:416-22.
94. Vennera Mdel C, Valero A, Uria E, Forne C, Picado C. Cost-effectiveness analysis of omalizumab for the treatment of severe persistent asthma in real clinical practice in Spain. Clin Drug Investig 2016;36:567-78.
95. Verma P, Randhawa I, Klaustermeyer WB. Clinical efficacy of omalizumab in an elderly veteran population with severe asthma. Allergy Asthma Proc 2011;32:346-50.
96. Vieira T, de Oliveira JF, da Graca 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.
97. Wittchen HU, Muhlig S, Klotsche J, Buhl R, Kardos P, Ritz T, et al. Omalizumab versus 'usual care': results from a naturalistic longitudinal study in routine care. Int Arch Allergy Immunol 2012;159:83-93.
98. Yorgancioglu A, Oner Erkekol F, Mungan D, Erdinc M, Gemicioglu B, Ozseker ZF, et al. Long-term omalizumab treatment: a multicenter, real-life, 5-year trial. Int Arch Allergy Immunol 2018;176:225-33.
99. Zazzali JL, Raimundo KP, Trzaskoma B, Rosen 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.
100. Zierau L, Walsted ES, Thomsen SF, Backer V. Response to omalizumab in patients with severe allergic asthma: a real-life study. Respir Med 2017;131:109-13.
101. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 2014;371:1189-97.
102. Chupp GL, Bradford ES, Albers FC, Bratton DJ, Wang-Jairaj J, Nelsen LM, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. Lancet Respir Med 2017;5:390-400.
103. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med 2014;371:1198-207.
104. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet 2016;388:2115-27.
105. Ferguson GT, FitzGerald JM, Bleecker ER, Laviolette M, Bernstein D, LaForce C, et al. Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med 2017;5:568-76.
106. Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. Chest 2016;150:789-98.
107. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 2015;3:355-66.
108. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med 2018;378:2486-96.
109. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med 2018;378:2475-85.
110. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention; 2019. Available from: https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf. Accessed February 2, 2020.
111. Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. J Allergy Clin Immunol 2009;124:1210-6.
112. Milgrom H, Berger W, Nayak A, Gupta N, Pollard S, McAlary M, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). Pediatrics 2001;108:E36.
113. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2016;388:2128-41.
114. Busse WW, Massanari M, Kianifard F, Geba GP. Effect of omalizumab on the need for rescue systemic corticosteroid treatment in patients with moderate-to-severe persistent IgE-mediated allergic asthma: a pooled analysis. Curr Med Res Opin 2007;23:2379-86.
115. Massanari M, Milgrom H, Pollard S, Maykut RJ, Kianifard F, Fowler-Taylor A, et al. Adding omalizumab to the therapy of adolescents with persistent uncontrolled moderate—severe allergic asthma. Clin Pediatr (Phila) 2009;48:859-65.
116. Nunes C, Pereira AM, Morais-Almeida M. Asthma costs and social impact. Asthma Res Pract 2017;3:1.
117. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med 2011;364:1005-15.
118. Corren J, Casale T, Deniz Y, Ashby M. Omalizumab, a recombinant humanized anti-IgE antibody, reduces asthma-related emergency room visits and hospitalizations in patients with allergic asthma. J Allergy Clin Immunol 2003;111:87-90.
119. Braido F, Baiardini I, Canonica GW. Patient-reported outcomes in asthma clinical trials. Curr Opin Pulm Med 2018;24:70-7.
120. Ledford D, Busse W, Trzaskoma B, Omachi TA, Rosen K, Chipps BE, et al. A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. J Allergy Clin Immunol 2017;140:162-169.e2.