

# Omalizumab for the Treatment of Inadequately Controlled Allergic Rhinitis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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**What is already known about this topic?** Several clinical trials have evaluated omalizumab in inadequately controlled allergic rhinitis by using various clinical outcomes and comorbidities. Despite a relative effect direction consistency, a systematic appraisal of the evidence that focuses on the assessed outcomes and their clinical importance is lacking.

**What does this article add to our knowledge?** Omalizumab is generally well-tolerated and associated with a statistically significant symptom relief, decreased rescue medication use, and improvement of quality of life in patients with inadequately controlled allergic rhinosinusitis.

**How does this study impact current management guidelines?** Combination therapy could be a meaningful improvement over current standard therapy for the complex cases of allergic rhinitis. Larger clinical trials and economic studies are needed to address issues of rare events occurrence and cost-effectiveness, respectively.

**BACKGROUND:** Patients with moderate-to-severe allergic rhinitis who are inadequately controlled despite treatment according to current rhinitis management guidelines have a significant unmet medical need. Such patients have a negative impact on daily functioning and are at risk of developing serious comorbidities, such as asthma and chronic rhinosinusitis. **OBJECTIVE:** To assess the efficacy and safety of omalizumab in poorly controlled allergic rhinitis under a meta-analysis framework.

**METHODS:** MEDLINE and the Cochrane Central Register of Controlled Trials were searched through September 2013. Studies on the efficacy of omalizumab in allergic rhinitis that assessed clinical outcomes were selected. Descriptive and quantitative information was extracted; mean differences and relative risk estimates were synthesized under a fixed or random effects model. Heterogeneity was assessed by using the Q statistic

and the I<sup>2</sup> metric. Subgroup analyses were performed for the presence of specific immunotherapy treatment.

**RESULTS:** Of the 352 citations retrieved, 11 studies of 2870 patients were finally included. A statistically significant reduction in the daily nasal symptom severity score (standardized mean difference  $-0.67$  [95% CI,  $-1.3$  to  $-0.31$ ];  $P < .0001$ ; I<sup>2</sup>, 92%) and a statistically significant reduction in daily nasal rescue medication score ( $-0.22$  [95% CI,  $-0.39$  to  $-0.05$ ;  $P = .01$ ; I<sup>2</sup>, 58%) were observed. There was not a statistically significant difference in the occurrence of any adverse event (relative risk 1.06 [95% CI, 0.94-1.19; I<sup>2</sup>, 55%).

**CONCLUSIONS:** Omalizumab is statistically significantly associated with symptom relief, decreased rescue medication use, and improvement of quality of life in patients with inadequately controlled allergic rhinosinusitis. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:332-40)

**Key words:** Omalizumab; Anti-IgE; Rhinosinusitis; Rhinitis; Meta-analysis

Allergic rhinitis (AR) is a highly prevalent condition that variably affects 20% to 50% of the general population.<sup>1</sup> Symptomatic AR has a negative impact on daily functioning and may result in absenteeism or reduced productivity and performance at work.<sup>2-7</sup> The Allergic Rhinitis and its Impact on Asthma guidelines recommend that, in addition to allergen avoidance and allergen immunotherapy, all other therapies are aimed at symptomatic relief.<sup>8</sup> New-generation oral H1 antihistamines and/or intranasal glucocorticosteroids remain the first-line treatment for AR. Nevertheless, there is a considerable proportion of patients with AR who fail to respond to standard therapy and remain a challenge in every day clinical practice. Given its

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#### Abbreviations used

AE- Adverse event  
AR- Allergic rhinitis  
DNSMS- Daily nasal symptom medication score  
DNSSS- Daily nasal symptom severity score  
DUAL- Dupinoid and Omalizumab bei Asthma Saisonale Study  
ITNG- Immune Tolerance Network Group  
ORSG- Omalizumab Rhinitis Study Group  
OSARTG- Omalizumab Seasonal Allergic Rhinitis Trial Group  
PAR- Perennial allergic rhinitis  
QoL- Quality of life  
RCT- Randomized controlled trial  
rQoL- Rhinosinusitis-related quality of life  
SAR- Seasonal allergic rhinitis  
SIT- Specific immunotherapy  
TNSS- Total nasal symptom score

pivotal role in the development of allergic conditions, IgE has been a candidate therapeutic target.<sup>9</sup> Omalizumab, a recombinant humanized IgG1 noncomplement-fixing monoclonal antibody achieves neutralization of IgE in humans, has been tested in several clinical trials, and its beneficial effect has been established in patients with poorly controlled allergic asthma.<sup>4-7,10,11</sup>

Several randomized controlled trials (RCT) evaluated omalizumab in AR (both seasonal and perennial).<sup>12-22</sup> However, the evidence that stems from the individual currently available randomized trials regarding the use of omalizumab in AR is not robust. Various clinical outcomes have been assessed, some in the presence of comorbidities (ie, allergic asthma),<sup>18,21</sup> whereas a few trials assessed omalizumab together with another form of anti-allergic treatment (ie, allergen immunotherapy).<sup>16,19,21,22</sup> Thus, several questions have been posed that pertain to the populations assessed in the published literature and their clinical characteristics, the dosing schemes implemented, and the clinical outcomes used along with their clinical importance that require systematic appraisal and quantitative synthesis of the accumulated randomized evidence. To address these questions, we conducted a systematic review and a meta-analysis of all published randomized trials that assessed the efficacy and safety of omalizumab in AR.

## METHODS

### Identification and eligibility of relevant randomized studies

We searched for randomized trials that assessed the safety and efficacy of omalizumab in AR. We searched PubMed (last search, September 2013) by using the term “omalizumab” (limits: clinical trial) and The Cochrane Library (2013, Chichester: Wiley) by using the terms “omalizumab or anti-IgE.” References of the retrieved articles also were screened. We set no language restrictions. We considered all randomized trials that assessed subcutaneous omalizumab as treatment or pretreatment for subsequent immunotherapy for AR. All nonrandomized trials were excluded. We also excluded studies that assessed clinical outcomes not related to rhinitis, such as skin test results, and studies that assessed nonclinical outcomes, such as IgE levels. Whenever reports pertained to the same patients at different follow-up periods, we retained for the main analysis the one with the longer follow-up to avoid duplication of information. Alternatively, whenever multiple reports pertained to the same

trial with different outcomes, we included all pertinent reports as long as there was no overlap in the provided information. Finally, whenever RCTs with multiple intervention and control arms were assessed, we retained for the analysis the placebo arm as the control group and the omalizumab arm closest to the US Food and Drug Administration approved dosage scheme as the active comparator. Personal communication with the investigators of published eligible reports was attempted whenever the available published information was not adequate for the analysis.

### Outcomes

The outcomes assessed in the systematic review and meta-analysis included clinical improvement of rhinitis symptoms, use of rescue medication, rhinosinusitis-related quality of life (rQoL), and the occurrence of adverse events (AE). Each study that assessed omalizumab was included in the systematic review and meta-analysis regardless of the type and number of outcomes used to evaluate the safety and efficacy of the intervention.

### Data extraction

We recorded information about study characteristics and demographics such as investigators, publication year, and journal; total and per-arm sample size; population characteristics; treatment indication; omalizumab dose and mode of administration; study duration; rhinitis-related outcome and definition thereof; use or not of pretreatment; the mean difference and standardized mean difference (and corresponding SE) for the parameters assessed as continuous outcomes, that is, daily nasal symptom severity score (DNSSS), relative risk (and corresponding 95% CI) for the parameters assessed as binary outcomes, such as the occurrence of any AE and information regarding methodologic aspects, such as randomization mode, allocation concealment, blinding, loss to follow-up, and intention-to-treat analysis. Data extraction was performed independently by 2 investigators (S.T., X.T.), and discrepancies were resolved by another (E.E.N.).

### Assessment of methodologic quality

We assessed the methodologic quality of the included trials and the risk of bias conferred thereof by using elements included in the Cochrane collaboration tool for assessing risk of bias.<sup>23</sup> The domains used in the present systematic review pertained to randomization and allocation concealment (selection bias), blinding (performance and detection bias), and lost to follow-up and adherence to the intention-to-treat principle (attrition bias). Among the established strategies, we chose to present the meta-analysis of all studies while providing a summary of the risk of bias across studies.

### Evidence synthesis

For each trial, we extracted or calculated the summary mean difference for the assessed scores (and 95% CI) and the relative risk for the occurrence of any AEs (along with the corresponding 95% CI). We also used the standardized mean difference (and 95% CI), which expresses the mean score improvement in SD units, and can be used to directly compare different scales or scores across the individual studies. The overall summary effect sizes were estimated with fixed and random effects models.<sup>24</sup> Random effects are more appropriate in the presence of between-study heterogeneity, provided that events are not rare. We tested for heterogeneity with the Q statistic (traditionally considered significant for  $P < .10$ )<sup>24</sup> and quantified its extent with the I<sup>2</sup>

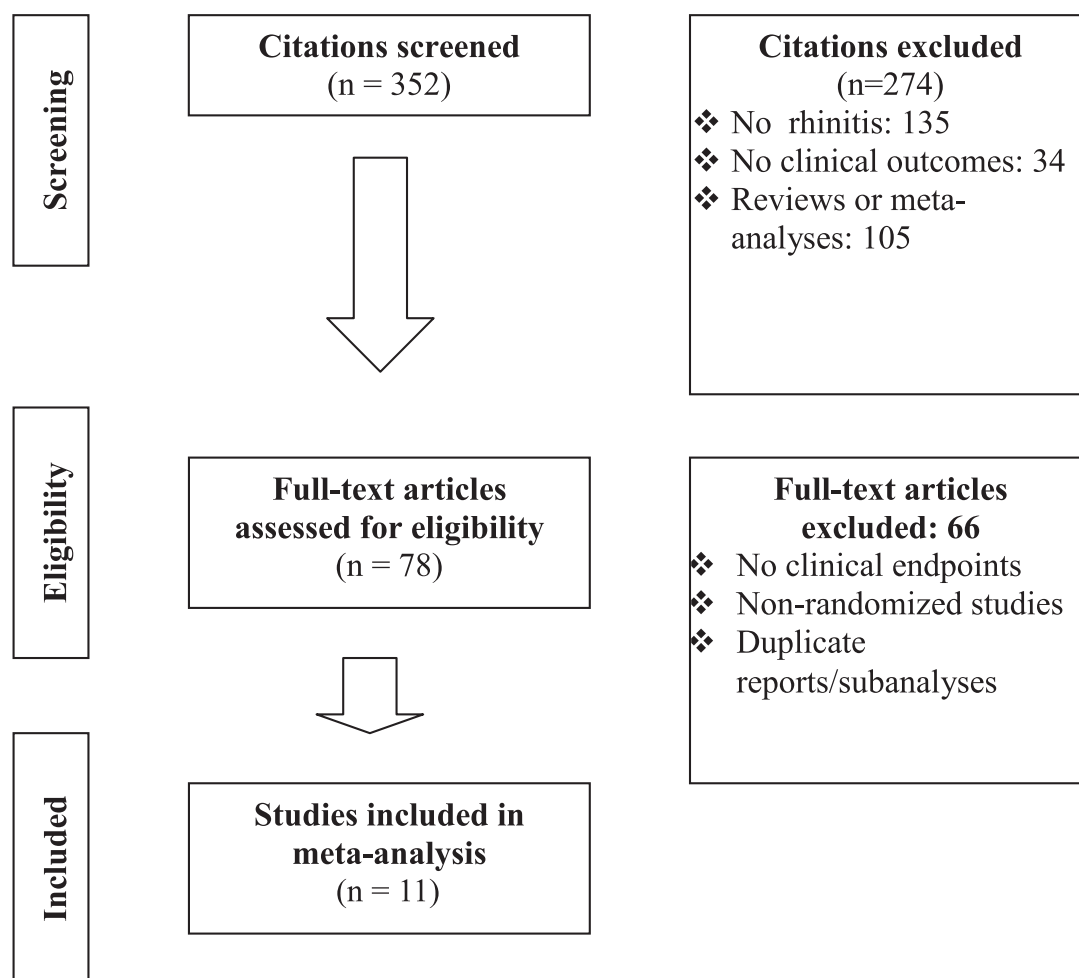


**FIGURE 1.** Flow chart for the selection of eligible studies (adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] flow-chart).

metric (range, 0%-100%), with values of more than 75% indicating considerable heterogeneity.

We performed analyses in *a priori* defined subgroups of trials to explain the observed between-study heterogeneity and to identify subgroup-specific differences in the effect of the intervention. We conducted separate analyses for trials using omalizumab with specific immunotherapy (SIT) and for trials in pediatric populations. To detect publication bias, we visually examined funnel plots per assessed outcome and further assessed asymmetry by using the Begg-Mazumbar test.<sup>25</sup> Analyses were conducted in STATA 10.0 (STATA Corp, College Station, Tex). All *P* values are 2 tailed, and *P* < .05 signifies statistical significance. The study is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist.<sup>26</sup>

## RESULTS

### Study selection

Briefly, of the 352 citations initially retrieved through the search algorithm, we finally included in our study 11 eligible clinical trials that assessed 2870 randomized patients (Figure 1).<sup>12-22</sup>

### Population and study characteristics

**Population and study characteristics.** A summary of the demographic and clinical characteristics of the eligible studies and populations are shown in Table I. Trials were published from 1997 to December 2010. The majority of the trials assessed patients of primarily European background including Northern American populations (8 studies with a total of 2462 participants) and of Japanese background (2 studies with 408 participants). The largest trial included 536 participants.<sup>15</sup> From a total of 2870 participants, 906 and 833 were randomized to receive omalizumab and as controls, respectively. Two publications that referred to the same clinical trial with a sample size of 221 patients included only children and adolescents ages 6-17 years, with a mean age of 12 years.<sup>16, 22</sup> Another 4 trials included pediatric patients; of these, 2 reported the proportion of the included pediatric patients (9%<sup>17</sup> and 23%,<sup>21</sup> respectively), whereas the other 2 did not provide further information.<sup>12,18</sup> The remaining 5 trials only included adult patients, with a mean age of 33 years. The proportion of male participants ranged from 33% to 53% across the 12 studies. Regarding the seasonal AR studies, all the patients were monosensitized. Only the patients of 2 seasonal AR studies were double sensitized (Table I). Regarding the perennial AR studies, patients were sensitized to

TABLE I. Characteristics of the included studies

| Study                               | Country                 | Year | Mean age (y) | Indication                                       | Omalizumab dose                                        | Control            | Mean DNSSS (placebo) | Follow-up, wk | N all | Outcomes assessed                                                                                                                                              |
|-------------------------------------|-------------------------|------|--------------|--------------------------------------------------|--------------------------------------------------------|--------------------|----------------------|---------------|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Casale et al <sup>13</sup>          | USA                     | 1997 | 34           | SAR, ragweed (+)                                 | 0.150 mg/kg every 2 wk                                 | Placebo            | 0.73                 | 12            | 240   | Average all daily SS, total days with symptoms, rescue medication, QoL (Juniper, SF-36), AE                                                                    |
| Adelroth et al <sup>14</sup>        | Sweden, Finland, Norway | 2000 | 33           | SAR, birch pollen (+)                            | 300 mg (0,4w) or 300 mg (0,3,6w)                       | Placebo            | 0.7                  | 8             | 251   | 7-symptom, 4-point scale, rescue medication, AE                                                                                                                |
| Casale et al (OSARTG) <sup>12</sup> | USA                     | 2001 | 34.5         | SAR, ragweed (+)                                 | 50, 150, or 300 mg every 3 wk                          | Placebo            | 0.75                 | 9             | 536   | DNSSS, rescue medication, AE                                                                                                                                   |
| Kuehr et al (ORSG) <sup>16*</sup>   | Germany                 | 2002 | 12†          | SAR, birch pollen (+), grass pollen (+)          | 0.016 mg/kg per IU/mL of IgE every 4 wk                | Placebo            | 0.24                 | 24            | 221   | DNSSS, rescue medication, AE                                                                                                                                   |
| Chervinsky et al <sup>17‡</sup>     | USA                     | 2003 | 34           | PAR, dust, dog or cat skin test (+)              | 0.016 mg/kg per IU/mL of IgE every 4 wk                | Placebo            | 1                    | 16            | 289   | DNSSS, rescue medication, rQoL, global evaluation, AE                                                                                                          |
| Vignola et al (SOLAR) <sup>18</sup> | Multi-center            | 2004 | 38.5         | Concomitant asthma and PAR                       | 0.016 mg/kg per IU/mL of IgE (IU/mL) per 4 wk          | Placebo            | NA                   | 28            | 405   | Wasserfallen rhinitis clinical symptom scores, rescue-medication use, rQoL evaluations, patient and investigator global evaluations of treatment effectiveness |
| Casale et al (ITNG) <sup>19*§</sup> | USA                     | 2006 | 33.3         | SAR, ragweed (+)                                 | 0.016 mg/kg per IU/mL of IgE (IU/mL) per 4 wk          | Placebo            | 0.69                 | 21            | 159   | Daily allergy SS, AE                                                                                                                                           |
| Okubo et al <sup>15</sup>           | Japan                   | 2006 | 32           | SAR, cedar pollen (+)                            | 150, 225, 300, or 375 mg every 2 to 4 w                | Placebo            | 1.88                 | 24            | 100   | DNSMS, DNSSS, rescue medication, AE                                                                                                                            |
| Nagakura et al <sup>20</sup>        | Japan                   | 2007 | 35.3         | SAR, cedar pollen (+)                            | 150, 225, 300, or 375 mg every 2 to 4 w                | Suplatast tosilate | 1.46                 | 12            | 308   | DNSMS, DNSSS, rescue medication, AE                                                                                                                            |
| Kopp et al (DUAL) <sup>21*</sup>    | Germany                 | 2008 | 30†          | Concomitant asthma and SAR, grass and/or rye (+) | Based on the patient's body weight and total serum IgE | Placebo            | 0.38                 | 20            | 140   | Mean daily symptom severity score, mean daily rescue medication, QoL                                                                                           |
| Kamin et al (ORSG) <sup>22*</sup>   | Germany                 | 2010 | 12           | SAR, birch pollen (+), grass pollen (+)          | Dependent on body weight and total serum IgE           | Placebo            | NA                   | 36            | 221   | AE                                                                                                                                                             |

+, positive; AE, adverse events; DNSMS, Daily nasal symptom medication score; DUAL, Depigoid und Omalizumab bei Asthma Saisonale study; ITNG, Immune Tolerance Network Group; Juniper, Juniper's asthma quality of life questionnaire; N, sample size; ORSG, Omalizumab Rhinitis Study Group; OSARTG, Omalizumab Seasonal Allergic Rhinitis Trial Group; PAR, perennial allergic rhinitis; RIT, Rush immunotherapy; SAR, Seasonal allergic rhinitis; SS, symptom score; SF-36, short form health survey 36; TNSS, Total nasal symptom score; w, week.

\*Plus SIT.

†Median.

‡Study reports from the Casale research group.

§Omalizumab was administered as pretreatment to RIT, RIT and immunotherapy + omalizumab vs immunotherapy.

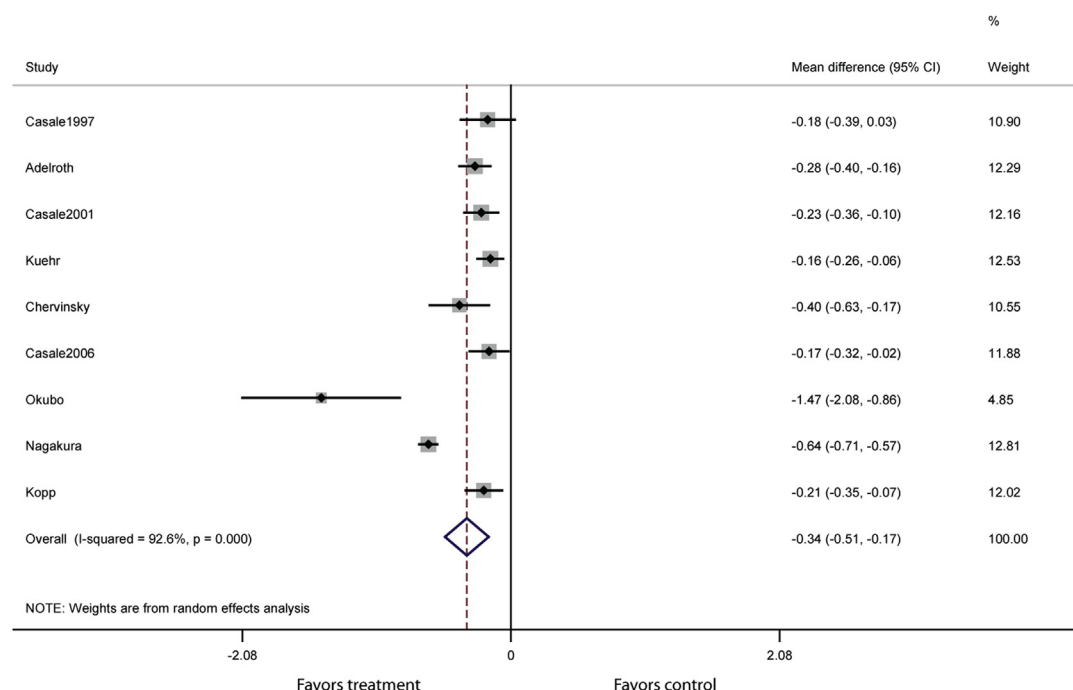


**FIGURE 2.** Efficacy of omalizumab in reducing the DNSSS. The horizontal lines represent 95% CIs of the mean difference estimates. The size of the squares that accompany the mean difference point estimate corresponds to the study weight in the random-effects meta-analysis. Diamonds represent the meta-analysis summary effect estimate.

house dust mites (*Dermatophagoides farinae* or *Dermatophagoides pteronyssinus*), cat, or dog (Table 1). More specifically, all the studies on seasonal AR enrolled patients with at least a 2-year history of inadequately controlled moderate-to-severe seasonal AR induced by grass, ragweed, birch, and cedar with or without mild allergic asthma and/or conjunctivitis with a positive allergen-specific skin prick test and raised serum allergen-specific IgE. Two studies enrolled patients who had moderate-to-severe perennial AR induced by one of the dust mites (*Dermatophagoides farinae* or *Dermatophagoides pteronyssinus*), dog, or cat.<sup>17,18</sup> Given that there was only 1 study that enrolled patients with perennial AR and provided DNSSS data for further analysis, a subgroup analysis was not feasible.

DNSSS, use of rescue medication, and AE were the outcomes more extensively assessed (8, 7, and 8 studies, respectively). The DNSSS is calculated as the mean symptom score across all 4 symptom severity components (sneezing, itchy, runny and stuffy nose), each scored by patients according to a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe). Each patient recorded individual symptom severity scores on a daily basis by using diary cards. The mean DNSSS in the placebo groups at the predefined follow-up time across all studies was 1.29. Most studies were of good methodologic quality (see Table E1 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)); 4 studies used an intention-to-treat analysis, and all studies were double blind, although methods used to ensure adequate allocation concealment and blinding were not clearly reported in most studies.

**Patient adherence.** In the overall population, 126 patients (7%) discontinued treatment, of whom 66 received omalizumab and 60 received placebo. Similar to the overall population, 1%

(17 patients), and 0.6% (11 patients) discontinued due to AEs and unsatisfactory treatment effect, respectively. One trial did not provide any data regarding discontinuation.<sup>27</sup>

**Dose regimen.** In all the studies, omalizumab was administered subcutaneously every 2 or 4 weeks to provide a dose of at least 0.016 mg/kg per IU/mL of IgE adjusted to body weight and baseline IgE levels by using a dosing table.<sup>14</sup> The participants received omalizumab for 8 to 24 weeks. The mean treatment duration was 16 weeks, and more than 90% of patients were exposed to omalizumab for 12 weeks. In all trials, anti-IgE treatment was administered 4 to 14 weeks before the expected culprit allergen pollen season. Pollen counts were assessed systematically in all but 1 center that contributed to this meta-analysis, and the start and the end of the pollen season were each defined as a threshold of  $>10$  grains/ $m^3$  per 24 hours for 3 consecutive days for birch, ragweed, and  $>5$  grains/ $m^3$  per 24 hours for grass. With regard to cedar, the start day of the pollen period was defined as the first of 2 consecutive days when  $\geq 1$  grain/ $cm^2$  was counted and the end day of the pollen period was the first of 3 consecutive days when no grain was counted. The efficacy analysis was based on diary information collected only during the defined pollen seasons. With regard to the perennial AR studies, the average daily nasal severity score was calculated by first taking the average of each patient's daily nasal severity score over the run-in period (baseline score), every month after the baseline visit (eg, scores for weeks 4, 8, 12, 16) over the entire treatment period. In 3 of 12 trials omalizumab was administered as add-on to SIT for ragweed, grass, birch pollen induced seasonal AR within at least the previous 2 years.<sup>16,19,21,22</sup>

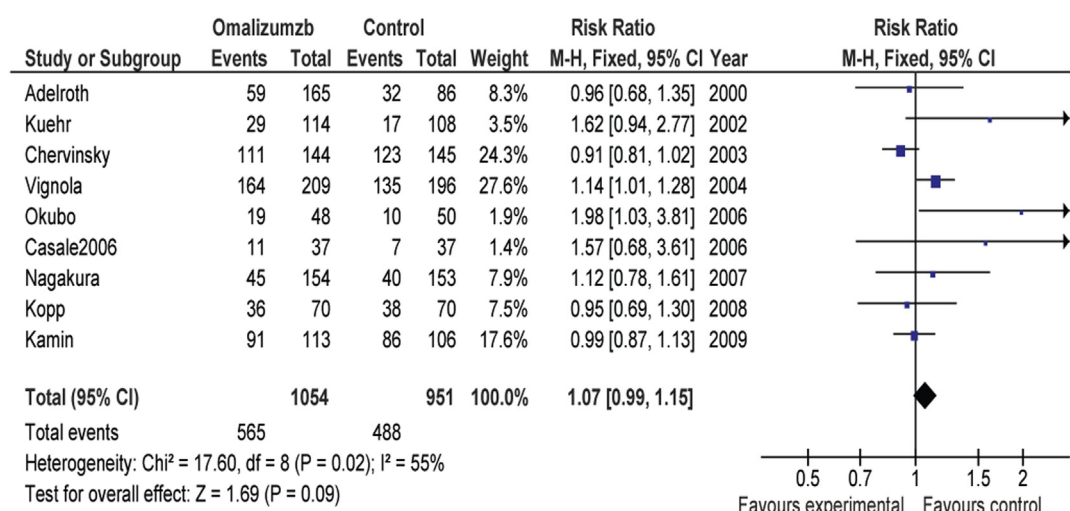


**FIGURE 3.** Forest plot of the meta-analysis of omalizumab for the occurrence of any AEs. The horizontal lines represent 95% CIs of the relative risk estimates. Diamonds represent the meta-analysis summary effect estimate.

## Assessed outcomes and evidence synthesis

**DNSSS.** Nine studies with 1753 randomized patients provided enough data to allow for a quantitative evidence synthesis based on the DNSSS.<sup>12-17,19-21</sup> Overall, omalizumab statistically significantly reduced the daily nasal severity symptom score by a summary mean difference of  $-0.34$  (95% CI,  $-0.51$  to  $-0.17$ ;  $P < .0001$ ;  $I^2$ , 92%) (Figure 2) and a standardized mean difference of  $-0.67$  (95% CI,  $-1.3$  to  $-0.31$ ;  $P = .0002$ ;  $I^2$ , 92%), which indicates a 0.67 decrease in DNSSS SD units. Based on the study that assessed perennial AR with available data, the categorical shift from baseline in average daily nasal symptom severity score during the entire 16-week treatment period significantly favored omalizumab versus placebo, with 69% versus 49% of patients, respectively, experiencing a decrease in symptom severity category with daily nasal severity scores categorized as follows: controlled, 0 to  $<0.75$ ; mild, 0.75 to  $<1.5$ ; moderate, 1.5 to  $<2.25$ ; and severe, 2.25 to 3.0.<sup>17</sup>

Visual inspection of the funnel plot indicated no asymmetry. After conducting separate analyses for trials using omalizumab with SIT and for trials in pediatric populations, the observed heterogeneity ( $P < .001$ ) could not be explained by the parallel use of SIT or the exclusion of studies in children.

**Use of rescue medication.** The type of rescue medication varied across the included studies, that is, systemic antihistamines (available in all studies), naphazoline nitrate as the decongestant drug, topical antihistamines, topical nasal corticosteroids, and systemic corticosteroids. A rescue medication use index (score) was calculated for each patient with seasonal AR by adding the total number of different kinds of rescue medications used each day during the pollen season and by dividing it by the total number of days in the pollen season. Information on the use of rescue medication was available in 9 studies. Nevertheless, the tools used to assess the use of rescue medication differed substantially among studies, including the proportion of tablet-using days and the mean daily nasal rescue medication scores. Three studies provided data on the mean daily nasal rescue medication scores to allow for a quantitative synthesis, one of a European ancestry and two of Asian ancestry ( $N = 545$  randomized

patients).<sup>15,20,21</sup> Overall, omalizumab reduced the use of rescue medication by a standardized mean difference of  $-0.22$  (95% CI,  $-0.39$  to  $-0.05$ ;  $P = .01$ ,  $I^2$ , 58%) and a mean difference of  $-0.05$  (95% CI,  $-0.09$  to  $-0.01$ ), which corresponded to the a 0.22 reduction of the SD for the assessed scores. Of note, the 2 studies that showed the largest effects for the rescue medication use score are the ones with the largest detected DNSSS differences, whereas the third study showed a null effect. The observed heterogeneity ( $P = .07$ ) was still present after the exclusion of the 1 European trial and the consideration of the 2 remaining Asian studies, whereas the results became nonsignificant when a random effects model was implemented, which suggests that, when the meta-analysis model involves an assumption that the effects being estimated in the different studies are not identical but follow some distribution, the overall result becomes statistically not significant.

With regard to the remaining studies that assessed rescue medication use but without adequate quantitative information, 4 showed statistically significant differences favoring omalizumab,<sup>12,14,16,17</sup> whereas 2 studies did not show a statistically significant difference.<sup>13,18</sup> An assessment that takes into consideration the magnitude of the effects across these studies was not feasible due to the different metrics used.

**Quality of life.** Two studies<sup>14,21</sup> provided data on QoL that would allow for a quantitative synthesis. Both studies showed a statistically significant association between omalizumab and an improvement of the QoL. Due to the scarcity of the data, a quantitative synthesis was deemed uninformative and was not conducted. Adelroth et al<sup>14</sup> reported a statistically significant difference in all aspects of the rQoL questionnaire as well as a clinically meaningful improvement, whereas Kopp et al,<sup>21</sup> in a study that assessed omalizumab in combination with SIT in patients with seasonal AR and comorbid seasonal allergic asthma incompletely controlled by conventional pharmacotherapy, also found a mild improvement in rQoL.

**Adverse events.** Most studies reported the number of patients who experienced any AEs. The relevant accumulated

**TABLE II.** Drug-related AEs in most frequently affected body systems

| System organ class and AEs*                                                                                                                | Omalizumab (N = 999),<br>frequency (%)† | Placebo (N = 713),<br>frequency (%)† |
|--------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|--------------------------------------|
| General disorders and administration site conditions (injection site, erythema, pain, hemorrhage, induration, pruritus, swelling, malaise) | 204 (20)                                | 94 (13)                              |
| Nervous system disorders (headache, somnolence)                                                                                            | 125 (13)                                | 96 (13)                              |
| Infections and infestations (nasopharyngitis, sinusitis)                                                                                   | 82 (8)                                  | 69 (7)                               |
| Respiratory, thoracic and mediastinal disorders (cough)                                                                                    | 153 (15)                                | 84 (12)                              |
| Gastrointestinal disorders (diarrhea)                                                                                                      | 29 (3)                                  | 24 (3)                               |
| Skin and subcutaneous tissue disorders (dry skin, rash, face edema)                                                                        | 55 (6)                                  | 20 (3)                               |
| Musculoskeletal system (back pain, arthralgia)                                                                                             | 22 (2)                                  | 17 (2)                               |

\*The symptoms in parentheses are the reported symptoms in the assessed studies.

†The frequency (%) corresponds to the main drug-related AE.

**TABLE III.** Drug-related serious AEs

| Study                               | Country                 | Year | No./total patients | Serious AEs                                     | Comments                                  |
|-------------------------------------|-------------------------|------|--------------------|-------------------------------------------------|-------------------------------------------|
| Casale et al <sup>13</sup>          | USA                     | 1997 | 1/240              | Colitis                                         | Unrelated to the drug according to author |
| Adelroth et al <sup>14</sup>        | Sweden, Finland, Norway | 2000 | 0/251              | —                                               | —                                         |
| Casale et al (OSARTG) <sup>12</sup> | USA                     | 2001 | na/536             | Not available                                   | —                                         |
| Kuehr et al (ORSG) <sup>16</sup>    | Germany                 | 2002 | 0/221              | —                                               | —                                         |
| Chervinsky et al <sup>17</sup>      | USA                     | 2003 | 0/289              | —                                               | —                                         |
| Vignola et al (SOLAR) <sup>18</sup> | Multicenter             | 2004 | 3/405              | Acute appendicitis, chest pain, mild depression | —                                         |
| Casale et al (ITNG) <sup>19</sup>   | USA                     | 2006 | 1/159              | Sprains and strains                             | —                                         |
| Okubo et al <sup>15</sup>           | Japan                   | 2006 | 1/100              | Colitis ulcerative                              | —                                         |
| Nagakura et al <sup>20</sup>        | Japan                   | 2007 | 1/308              | Ureteric calculus                               | Unrelated to the drug according to author |
| Kopp et al <sup>21</sup>            | Germany                 | 2008 | 0/140              | —                                               | —                                         |

ITNG, Immune Tolerance Network Group; na, not available; ORSG, Omalizumab Rhinitis Study Group; OSARTG, Omalizumab Seasonal Allergic Rhinitis Trial Group.

evidence assessed 1053 patients who experienced any AEs across a total of 2005 randomized patients. There was no statistically significant association between the occurrence of any AE and omalizumab (summary relative risk 1.07 [95% CI, 0.99-1.15;  $P = .09$ ;  $I^2$ , 55%) (Figure 3); yet we have to acknowledge that the accumulated randomized evidence is underpowered to detect rare, life-threatening AEs. The most frequently reported AEs according to the system organ class in both groups are presented in Table II, accounting for general disorders and administration site disorders (mainly injection site erythema), nervous system disorders (mainly headache), and respiratory disorders (mainly cough). The diversity of the reporting of the observed AEs prevented a subgroup analysis based on the type of the AE. Serious AEs are presented in Table III. Of the included studies, none reported anaphylactic reactions or the detection of anti-omalizumab antibodies.

## DISCUSSION

In the present systematic review and meta-analysis, the available published randomized evidence on the safety and efficacy of omalizumab in poorly controlled seasonal and perennial allergic rhinoconjunctivitis across 11 RCTs, and 2870 patients were systematically assessed. Our meta-analysis showed that, in seasonal and perennial allergic rhinoconjunctivitis, treatment with omalizumab provides an improvement of DNSSS and a reduction of antiallergic medication use compared with placebo. The

rQoL also appears to be improved in the limited randomized evidence available. The observed safety profile indicates adequate tolerability and a comparable overall AEs pattern, although the available evidence still lacks the power to detect uncommon AEs.

To our knowledge, this is the first meta-analysis on the use of omalizumab for the treatment of AR. Systematic reviews and meta-analysis in other allergic conditions are in accordance with our findings.<sup>27-30</sup> In a meta-analysis of clinical trials of participants with chronic asthma,<sup>28</sup> omalizumab was significantly more effective than placebo at decreasing clinically significant exacerbations. When QoL indices were assessed for allergic asthma in 6 RCTs,<sup>27</sup> add-on therapy with omalizumab improved QoL to a significant and clinically meaningful level in patients with severe persistent allergic asthma. Finally, a recent meta-analysis in pediatric patients with asthma,<sup>30</sup> showed an acceptable safety profile for omalizumab, with a risk of AEs similar to placebo. Nevertheless, in economic analyses in adult and pediatric populations,<sup>30-32</sup> the results from the implemented models indicated that omalizumab, in addition to standard therapy, did not appear cost effective and that the projected cost-effectiveness ratios could fall within a favorable range if the cost of omalizumab decreased significantly, although, as the baseline patient asthma attack rate increased, the projected cost-effectiveness ratios improved considerably.

In our study, we did not observe statistically significant differences among studies in which omalizumab was administered alone or in combination with SIT. Although the observed

omalizumab effect was milder in studies in which SIT was coadministered (see Figure E1 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)), the heterogeneity was minimal among these 3 studies. This observation suggests that combination therapy could be a meaningful improvement over current standard therapy for the complex cases of AR, for example, patients with multiple allergic symptoms incompletely controlled by conventional pharmacotherapy or immunotherapy. Patients who were polysensitized might have an enhanced IgE immune response, as shown by higher serum levels of total and specific IgE, and SIT appears to be less effective than single-allergen SIT.<sup>1,2</sup> Anti-IgE reduces the immune response by decreasing levels of free IgE in the serum within hours to approximately 10 IU/mL,<sup>33</sup> which results in a better efficacy of SIT and adequate symptom control and reduction of acute allergic reactions induced by SIT.

The reported treatment-related overall AEs occurred in comparable rates for patients on omalizumab and patients treated with placebo. AEs compatible with hypersensitivity reactions, serum sickness syndrome, and anaphylaxis were generally uncommon, and no cases of malignancy, Churg-Strauss syndrome, or helminthic infection were observed in patients who received omalizumab. Only a minority of serious AEs that led to withdrawal were reported by the studies included in the meta-analysis, which confirms omalizumab as a safe procedure with limited, mostly mild, AEs. No anaphylactic reactions were reported in the assessed trials. The low incidence of anaphylaxis in this analysis is consistent with that reported in a review of data from previous clinical trials in adults and adolescents,<sup>9</sup> although anaphylactic reactions fall within the range of rare, life-threatening events that require very large sample sizes to be assessed appropriately and are, in addition, quantified by passive and active surveillance systems. Results of postmarketing reports based on an estimated exposure of approximately 57,000 patients have indicated that anaphylactic reactions do occur in approximately 0.2% of patients, mostly (approximately 60%) within 2 hours of the injection.<sup>34-36</sup>

Our study has certain limitations. Differences in the baseline severity of the disease; different prevalence of patients with other comorbidities, such as asthma, conjunctivitis, and atopic dermatitis; difficulties in the comparability of different scores used; differences in the pharmaceutical preparations; and differences in the SIT protocols among studies may have limited the accuracy of this meta-analysis.<sup>26</sup> We attempted to control for these differences by including parameters that described the patients studied and the study design features. However, these summary results describe only between-study, not between-patient, variation because they reflect group averages rather than individual data. Moreover, the assessed clinical outcomes are not independent but show correlation of varying magnitude. For example, the 2 studies that showed the largest effects for the rescue medication use score are also the ones with the largest detected DNSSS differences, whereas the third study showed a null effect. Finally, our findings come from published evidence, including small RCTs. Publication and language bias is a major concern when dealing with efficacy trials, but the assessed studies were published from 1997 to 2010, pertain to a cumulative sample size of more than 2000 randomized patients, and include several studies; furthermore, to enhance comprehensiveness, our searches were extended to the Cochrane Controlled Trials' Registry, which is built from multiple large databases.<sup>37</sup>

Although, the observed funnel plots showed symmetry, we cannot predict the effect of the incorporation of unpublished evidence and how much it could alter the status of the evidence. Moreover, although randomized evidence is protected from selection bias, performance and detection bias could be operating in the field. All the eligible trials were double blind and placebo controlled; yet, the reporting of the measures taken to safeguard the blinding process is far from adequate in the analyzed trials and leaves considerable uncertainty regarding important mythologic aspects of the trials.<sup>38</sup>

To conclude, omalizumab is generally well tolerated and significantly associated with symptom relief, decreased rescue medication use, and improved QoL in patients with inadequately controlled allergic rhinosinusitis refractory to conventional treatment. The potential benefits of omalizumab need to be considered in the context of costs of therapy and rare AEs. Larger clinical trials and economic studies are needed to address issues of rare events occurrence and cost-effectiveness, respectively.

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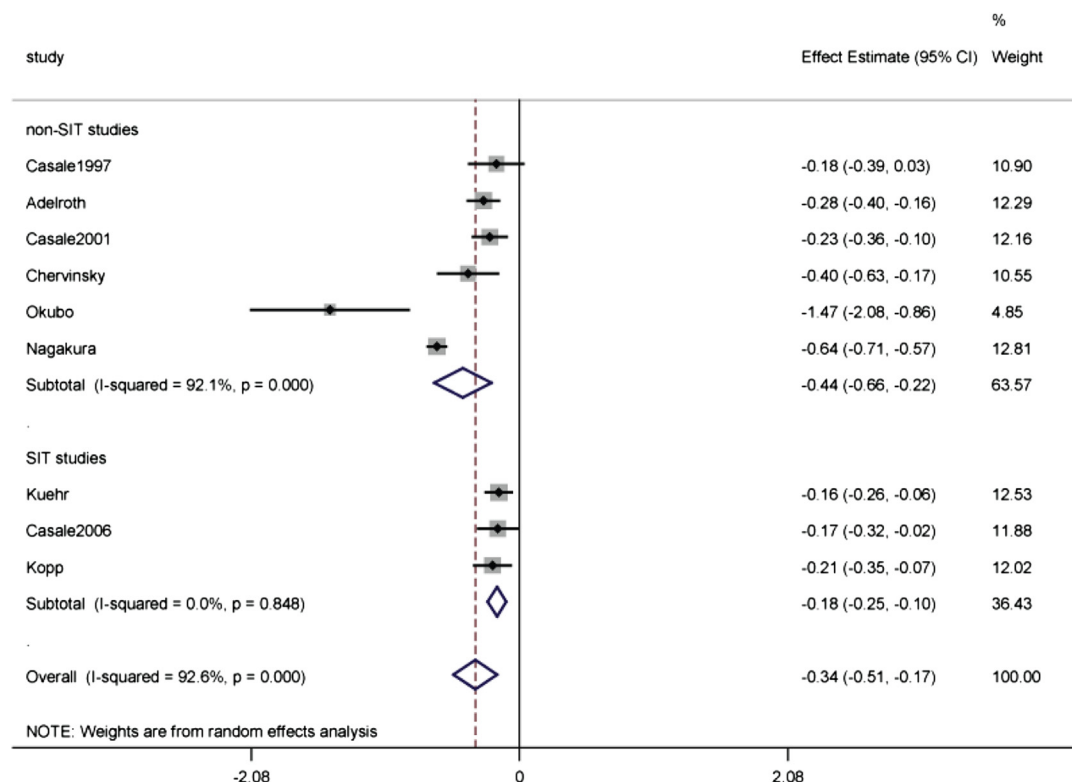


FIGURE E1. Meta-analysis results for studies in which SIT was or was not coadministered.

TABLE E1. Study characteristics related to the risk of bias

| First author                        | Y    | Randomization, done/described* | Allocation concealment, done/described* | Blinding, done/described* | Outcome assessment blinding, done/described* | Loss to follow-up described/ITT analysis* |
|-------------------------------------|------|--------------------------------|-----------------------------------------|---------------------------|----------------------------------------------|-------------------------------------------|
| Casale et al <sup>13</sup>          | 1997 | Yes/clear                      | No/clear                                | Yes/clear                 | Yes/unclear                                  | Yes/no                                    |
| Adelroth et al <sup>14</sup>        | 2000 | Yes/unclear                    | No/clear                                | Yes/unclear               | No/unclear                                   | Yes/yes                                   |
| Casale et al (OSARTG) <sup>12</sup> | 2001 | Yes/clear                      | No/clear                                | Yes/clear                 | Yes/clear                                    | Yes/no                                    |
| Kuehr et al (ORSG) <sup>16</sup>    | 2002 | Yes/unclear                    | No/clear                                | Yes/unclear               | No/unclear                                   | Yes/yes                                   |
| Chervinsky et al <sup>17</sup>      | 2003 | Yes/clear                      | Yes/clear                               | Yes/clear                 | Yes/unclear                                  | Yes/yes                                   |
| Vignola et al <sup>18</sup>         | 2004 | Yes/clear                      | No/clear                                | Yes/unclear               | No/unclear                                   | Yes/yes                                   |
| Casale et al (ITNG) <sup>19</sup>   | 2006 | Yes/unclear                    | No/unclear                              | Yes/unclear               | Yes/unclear                                  | Yes/no                                    |
| Okubo et al <sup>15</sup>           | 2006 | Yes/unclear                    | No/clear                                | Yes/unclear               | No/clear                                     | Yes/no                                    |
| Nagakura et al <sup>20</sup>        | 2007 | Yes/unclear                    | No/clear                                | Yes/unclear               | No/clear                                     | Yes/no                                    |
| Kopp et al <sup>21</sup>            | 2008 | Yes/clear                      | No/unclear                              | Yes/unclear               | No/unclear                                   | Yes/no                                    |
| Kamin et al <sup>22</sup>           | 2010 | Yes/unclear                    | No/unclear                              | Yes/unclear               | No/unclear                                   | No/no†                                    |

ITNG, Immune Tolerance Network Group; ITT, intention to treat analysis; ORSG, Omalizumab Rhinitis Study Group; OSARTG, Omalizumab Seasonal Allergic Rhinitis Trial Group.

\*Items that indicate low risk of bias are in green; items that indicate high risk of bias are in red.

†Safety assessment only.

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