Original Article

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^2 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^2, 92%) and a statistically significant reduction in daily nasal rescue medication score (−0.22 [95% CI, −0.39 to −0.05; $P = .01$; I^2, 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^2, 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.[1] Symptomatic AR has a negative impact on daily functioning and may result in absenteeism or reduced productivity and performance at work.[2-7] 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.[8] 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- Depigoid und OmalizUmab bei Asthma SaisonaL 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.[9] 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.[4-7,10,11]

Several randomized controlled trials (RCT) evaluated omalizumab in AR (both seasonal and perennial).[12-22] 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),[18,21] whereas a few trials assessed omalizumab together with another form of antiallergic treatment (ie, allergen immunotherapy).[16,19,21,22] 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 where 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.[23] 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.[24] 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 $P < .10$)[24] and quantified its extent with the I^2