Original Article

"Real-life" Effectiveness Studies of Omalizumab in Adult Patients with Severe Allergic Asthma: Meta-analysis

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What is already known about this topic? Omalizumab improves outcomes in patients with severe allergic asthma in randomized clinical trials.

What does this article add to our knowledge? Omalizumab, as add-on treatment to inhaled corticosteroid ± long-acting β_2-agonists agents, improves outcomes in patients with severe allergic asthma under conditions of heterogeneity in patients, clinicians, sites, and treatment patterns in "real-life" studies.

How does this study impact current management guidelines? Omalizumab, as an add-on therapy, is an effective treatment for patients with severe allergic asthma who do not respond sufficiently to prior treatment.

BACKGROUND: After the approval of omalizumab for severe allergic asthma, a total of 25 studies have evaluated the effectiveness of omalizumab under "real-life" conditions of heterogeneity in patients, clinicians, sites, and treatment patterns.

OBJECTIVE: We conducted a meta-analysis to evaluate the effectiveness of omalizumab focusing on treatment response, lung function, quality of life, symptom control, corticosteroid use, and exacerbations and hospitalizations at 4-6, 12, and 24 months.

METHODS: We searched PubMed and Embase for real-life studies on omalizumab in severe asthma published up to 2015. Three effect size types were extracted: single-point proportions; mean ± SD of change relative to baseline as raw numbers and standardized as Cohen's *d*; and changes in proportions of patients as relative risk. Random-effects meta-analyses were performed to account for within- and between-study heterogeneity. Studies were weighted by the DerSimonian and Laird method.

RESULTS: Per data available at the 3 time points, omalizumab therapy was consistently associated with large proportions of patients classified as "good" to "excellent" treatment responders (Global Evaluation of Treatment Effectiveness scale); improvements in forced expiratory volume in 1 second, quality of life (Asthma-related Quality-of-Life Questionnaire scale), and asthma symptom control (Asthma Control Test scale); reductions in oral and inhaled corticosteroid (ICS) use; and reductions in exacerbations and hospitalizations.

CONCLUSIONS: This meta-analysis of noncontrolled studies documents the real-life pharmacotherapeutic effectiveness of omalizumab, as add-on treatment to ICS ± long-acting β_2-agonists agents, in improving outcomes in patients with severe allergic asthma under conditions of heterogeneity in patients, clinicians, sites, and treatment patterns. The results mirror, complement, and extend the efficacy data from randomized controlled trials. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Omalizumab; Allergic asthma; IgE; Meta-analysis; Effectiveness*

Asthma affects up to 16% of people worldwide, much of which is due to a significant increase in incidence over the past 4 decades.[1-3] In the absence of a cure, the main treatment goal is asthma control to improve respiratory function; prevent exacerbations, unscheduled outpatient and emergency department visits, and hospitalizations; reduce the need for oral and inhaled corticosteroid (ICS) therapy; and thus improve quality of life.[2,4] Despite guidelines, the majority of patients are controlled suboptimally, especially those with severe asthma.[5,6]

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Abbreviations used
ACT- Asthma Control Test
AQLQ- Asthma-related Quality-of-Life Questionnaire
FEV_1- Forced expiratory volume in 1 second
GETE- Global Evaluation of Treatment Effectiveness scale
ICS- Inhaled corticosteroid
OCS- Oral corticosteroid
RR- Relative risk

Problematic severe asthma refers to asthma and asthma-like symptoms that remain uncontrolled despite high-intensity treatment, and comprises "difficult asthma" and "severe refractory asthma."[7] Difficult asthma is severe asthma due to factors unrelated to the disease such as patient noncompliance, psychosocial factors, functional breathing or vocal cord impairment, environment exposure, or undertreated comorbidities.[7] It is estimated to affect 17.4% of adult patients with asthma.[8] Severe asthma not associated with any of these factors is classified as severe refractory asthma. It is defined as the presence of poorly controlled asthma symptoms and/or frequent severe exacerbations despite high-intensity treatment, or to asthma that can only be controlled with systemic corticosteroids. The prevalence is estimated at 3.6% of adult patients with asthma.[8]

One target in asthma treatment is to control the endogenous antibodies associated with allergic reactions such as IgE antibodies.[9] Omalizumab is a recombinant monoclonal anti-IgE antibody that inhibits IgE binding sites[10,11] and thus the activation of mast cells and the release of inflammatory mediators.[9] Omalizumab is used as an add-on treatment to long-acting β_2-agonists and ICS.[12]

Phase III randomized clinical trials have shown omalizumab to improve asthma symptoms, reduce exacerbations, and improve quality of life.[13,14] Efficacy and safety data from these and subsequent studies have been reviewed elsewhere.[12,15-17] After regulatory approval, the "real-life" effectiveness of omalizumab under conditions of greater heterogeneity in patients, clinicians, and treatment regimens has been evaluated extensively. In a recent systematic review of 24 "real-life" effectiveness studies conducted worldwide and published between 2008 and 2015, we concluded that adjuvant omalizumab therapy is associated with improvements across the full spectrum of objective and subjective indicators that may extend up to 2 to 4 years.[18] This systematic review presented an overview of the studies conducted, and the outcomes observed. These outcomes were presented as a range from lowest to highest, however, without any justification. Here we follow up on this review with a meta-analysis of these 24 studies—plus 1 study published after the submission of our review for a total of 25—to quantitatively evaluate the "real-life" effectiveness of omalizumab in adult patients.

MATERIALS AND METHODS

Search strategy

We searched the PubMed and Embase databases for relevant published studies using the keywords "allergic asthma," "IgE," "omalizumab," "observational," "effectiveness," and "real-life." The first report on the effectiveness of omalizumab was published in 2008; thus, the search was limited from January 1, 2007, to December 31, 2015 (ahead-of-print) publications. In addition, the reference list of each manuscript retained was searched to identify other potential studies of relevance. Published conference abstracts were tracked for full publications. Studies included were those that were observational in design and included at least one metric of effectiveness in common with one or more additional studies and at a concurrent time point of exposure to omalizumab (eg, 4-6, 12, and/or 24 months). A total of 25 observational studies including 9213 patients across 32 countries[19-43] were identified, the 24 being included in our systematic review and 1 published after submission of our review.[18]

Data extraction

Each study was evaluated by at least 2 reviewers. We developed and pilot-tested a data extraction tool per standard meta-analysis methodology. Any discrepancies were reconciled among the reviewers or, if not reconciled, escalated to a third person.

Outcomes

Studies differed in the outcomes measured. In several studies, physicians were asked to rate the effectiveness of omalizumab using the Global Evaluation of Treatment Effectiveness (GETE) scale. This scale rates a patient's overall response to treatment as being excellent, good, moderate, poor, or worsening. A GETE of good or excellent was used in several studies as an index of responsiveness, and rationale for continuing omalizumab treatment, particularly after 4 months. Another common measure across multiple studies was the forced expiratory volume in 1 second (FEV_1), which is included in this meta-analysis as the percentage of expected. Subjective asthma-related quality of life was often assessed using the Asthma-related Quality-of-Life Questionnaire (AQLQ).[44] A change of 0.5 points on the 7-point AQLQ scale represents a clinically meaningful improvement in asthma-related quality of life. Asthma control was also frequently assessed using the Asthma Control Test (ACT),[45] a questionnaire with an overall score ranging from 5 (poorly controlled asthma) to 25 (well-controlled asthma). Also included in this meta-analysis were the proportion of patients requiring oral corticosteroids (OCS) or the amount of ICS required in beclomethasone equivalents as specified in the studies and matched each study's period of observation. Exacerbations were reported as the proportion of the sample that was exacerbation free and in annualized incidence rates. Asthma-related hospitalizations were reported in annualized incidence rates as well.

Statistical analysis

Our approach to this meta-analysis was guided by recommended analytic and reporting criteria.[46] Raw published/publically available data were extracted, verified in duplicate, and combined into a single database. Three effect size types were extracted from the literature. First, single-point estimates, such as the proportion of patients with a good or excellent GETE versus those without, were extracted as the number of successes versus total sample size. Second, mean improvements relative to a known baseline, such as improvements in FEV_1 or AQLQ, were extracted as mean change and the standard deviation of change or as raw pretreatment and posttreatment means and standard deviations. Standardized mean differences (Cohen's *d*)[47] were calculated as the primary metric for continuous measures; mean changes are also presented in the original metric for interpretability. Interpretation-wise, a Cohen's *d* of 0.2 is considered a small, 0.5 a medium, and 0.8 a large effect. Third, the number of patients requiring OCS at a given time point relative to the number of patients requiring OCS before the initiation of omalizumab was calculated in the metric of relative risk (RR).