

Omalizumab

A Review of its Use in the Treatment of Allergic Asthma

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Data Selection

Sources: Medical literature published in any language since 1980 on 'omalizumab', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE, EMBASE and AdisBase search terms were 'omalizumab' or 'monoclonal antibody E25'. Searches were last updated 6 May 2008.

Selection: Studies in patients with allergic asthma who received omalizumab. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Omalizumab, allergic asthma, monoclonal antibody, pharmacodynamics, pharmacokinetics, pharmacoeconomics, therapeutic use, tolerability.

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Summary

Abstract

Omalizumab, a monoclonal antibody that targets circulating IgE, is approved as add-on therapy for adult and adolescent patients with severe allergic asthma in the EU and moderate to severe allergic asthma in the US. Several randomized, double-blind trials have demonstrated the therapeutic efficacy of subcutaneously administered omalizumab as add-on therapy in patients with allergic asthma. The INNOVATE study included only patients with severe persistent disease, and omalizumab was associated with a statistically significant relative reduction of 26% in the rate of clinically significant asthma exacerbations (primary endpoint) compared with placebo (after adjustment for an imbalance in the exacerbation history at baseline). Results for a number of secondary outcomes also significantly favored omalizumab over placebo. Two large studies in patients with moderate to severe allergic asthma showed that, compared with placebo, omalizumab was associated with statistically significant relative reductions of 41–58% in the mean number of asthma exacerbations (primary endpoint) during the trial. Omalizumab also significantly reduced asthma symptom scores and the use of inhaled corticosteroids and rescue medication. Moreover, all of these trials showed that omalizumab was associated with clinically and statistically significant improvements from baseline in overall asthma-related quality of life.

In general, omalizumab was well tolerated in clinical trials. Most adverse events were mild or moderate in severity and occurred at a similar frequency among omalizumab and placebo recipients. Injection-site reactions were the most commonly reported adverse events in clinical trials with omalizumab. Although rare, anaphylactic reactions have occurred following administration of omalizumab, and appropriate precautions should be taken.

Results of several large randomized trials, therefore, have established omalizumab as an effective and well tolerated agent for use as add-on therapy in patients with severe persistent allergic asthma (EU labeling) or those with moderate to severe disease (US labeling). In addition, international treatment guidelines acknowledge the importance of omalizumab as a treatment option in these difficult-to-treat patient populations.

Pharmacological Properties

Omalizumab is a humanized IgG monoclonal antibody that improves the control of allergic asthma by binding to the Cε3 domain of free IgE, thereby inhibiting the binding of IgE to the surface of mast cells and basophils, reducing the release of inflammatory mediators. In patients with moderate to severe allergic asthma, treatment with omalizumab for ≈6 months decreased serum free IgE levels by 89–99% from baseline.

Subcutaneously administered omalizumab has a mean absolute bioavailability of 62%. Absorption into the systemic circulation is slow, with peak serum concentrations achieved after a mean of 7–8 days. Omalizumab exhibits linear pharmacokinetics at approved dosage regimens. IgG clearance processes, as well as specific binding and complex formation with IgE, are involved in omalizumab clearance. The mean elimination half-life of omalizumab is 26 days.

Therapeutic Efficacy

The clinical efficacy of subcutaneously administered omalizumab as add-on therapy in patients with allergic asthma has been demonstrated in several well designed trials. The 28-week, randomized, double-blind INNOVATE study in patients with severe persistent disease showed a statistically significant relative reduction of 26% in the rate of clinically significant asthma exacerbations (primary endpoint) with omalizumab compared with placebo (after adjustment for an imbalance in exacerbation history at baseline). Results for a number of secondary outcomes, including reduction in the rate of severe exacerbations and improvement in Asthma Quality of Life Questionnaire (AQLQ) scores, also significantly favored omalizumab over placebo.

In two large randomized, double-blind trials in patients with moderate to severe allergic asthma, omalizumab was associated with statistically significant relative reductions of 41–58% compared with placebo in the mean number of asthma exacerbations (primary endpoint) during the 16-week stable-corticosteroid phase and the 12-week corticosteroid-reduction phase of the trials. Both studies also showed that omalizumab significantly reduced asthma symptom scores, inhaled corticosteroid dosage, and rescue medication use compared with placebo. Mean improvement from baseline in overall AQLQ scores was also significantly greater among omalizumab than placebo recipients.

These data are supported by results of a smaller randomized, double-blind trial and a randomized, open-label (naturalistic) study in patients with moderate to severe asthma. In addition, results of the SOLAR trial in patients with concomitant moderate to severe allergic asthma and persistent allergic rhinitis showed significant improve-

ment in the co-primary endpoint of asthma exacerbation rate and asthma- and rhinitis-related quality of life among omalizumab-treated patients compared with those who received placebo.

Tolerability

Omalizumab was generally well tolerated in clinical trials, with most adverse events being mild or moderate in severity and reported with a similar frequency to those in placebo or control groups. The most frequently reported adverse events with omalizumab in clinical trials were injection-site reactions (45%), viral infection (23%), upper respiratory tract infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%). Anaphylactic reactions have occurred with omalizumab, usually (but not always) within 2 hours after administration of the first or subsequent doses. Although the incidence of anaphylaxis is low (≈ 0.1 – 0.2%), a boxed warning regarding anaphylaxis appears in US prescribing information, and appropriate precautions should be taken.

1. Introduction

Asthma is a chronic inflammatory disorder of the airways that affects an estimated 300 million individuals worldwide.^[1] The presence of chronic airway inflammation, which is a consistent feature of asthma, is associated with airway hyperresponsiveness that leads to the characteristic clinical symptoms of the disease, such as recurrent episodes of wheezing, breathing difficulties, chest tightness, and coughing.^[1–3] While the clinical manifestations of asthma can usually be controlled with appropriate treatment, an estimated 15 million disability-adjusted life-years are lost each year globally due to the disease.^[1]

Both genetic and environmental factors play a role in the development of asthma, and many different cells are involved in the expression of the disease.^[1–3] The pattern of inflammation in the airways appears to be similar whether patients have allergic or non-allergic asthma.^[1] Activation of mucosal mast cells and increased numbers of activated eosinophils, T-cell receptor invariant natural-killer T cells, and T helper 2 lymphocytes in the airways leads to the release of various mediators of bronchoconstriction and inflammation (e.g. histamine, leukotrienes, cytokines) that contribute to clinical symptoms.

Omalizumab (Xolair®)¹ is a subcutaneously administered, humanized IgG monoclonal antibody that binds to the high-affinity receptor binding (Cε3) domain of free IgE, thereby preventing IgE from binding to effector cells.^[4,5] In the EU, omalizumab is approved as add-on therapy for adults and adolescents with severe allergic asthma not adequately controlled with high-dose inhaled corticosteroids (ICSs) plus a long-acting β₂-agonist, and patients must be assessed by their physician 16 weeks after starting omalizumab to determine whether continued treatment with the drug is warranted (on the basis of whether a marked improvement in overall asthma control is observed).^[4] In some countries, such as the US, labeling for omalizumab is less restrictive, and the drug is approved for use in patients with moderate to severe allergic

asthma (section 7).^[5] This article provides an overview of the pharmacology of omalizumab and focuses on the therapeutic efficacy and tolerability of the drug in clinical trials.

2. Pharmacodynamic Properties

As a consequence of binding to the Cε3 domain of free IgE, omalizumab inhibits the binding of IgE to the high-affinity FCεRI receptor on the surface of mast cells and basophils.^[4–7] The resulting reduction in surface-bound IgE limits the allergic response by reducing the release of inflammatory mediators, such as leukotrienes, cytokines, and histamine. Since omalizumab does not bind to IgE that is already bound to mast cells or basophils, the onset of clinical activity is somewhat delayed,^[7] although well designed clinical trials showed benefits versus placebo after 4 weeks (section 4).^[8,9] Omalizumab also reduces the number of FCεRI receptors on basophils in atopic patients^[5] and prevents IgE-induced upregulation of FCεRI levels on human skin mast cells^[10,11] and airway mucosal cells (presumably mast cells).^[12]

At approved dosage regimens of omalizumab in patients with moderate to severe allergic asthma, serum free IgE levels decreased from baseline by 89–99% after ≈ 6 months of treatment.^[8,9] Serum total IgE levels (free plus bound IgE) increase during omalizumab therapy,^[9] which is attributed to a reduced clearance rate of complexed omalizumab : IgE compared with free IgE.^[5] After 16 weeks of omalizumab treatment, mean serum total IgE levels are approximately 5-fold higher than baseline levels and can take up to 1 year to return to pretreatment levels following discontinuation of omalizumab.^[4,5] Consequently, although baseline serum total IgE levels are used in determining initial omalizumab dosage regimens, serum total IgE levels cannot be used to assess further dosage requirements after lapses in omalizumab treatment of <12 months (section 7).

Omalizumab also appears to suppress the effects of exposure to allergens, thereby reducing chronic inflammation in the airways of

1 The use of trade names is for product identification purposes only and does not imply endorsement.

patients with allergic asthma.^[7] The effect of omalizumab on airway inflammation was demonstrated in a 16-week placebo-controlled study in 45 patients with allergic asthma who underwent bronchoscopic evaluations before and after treatment.^[12] Compared with placebo, omalizumab was associated with reductions in serum free IgE levels, the number of IgE-bearing cells in airway mucosa, and the number of cells positive for the high-affinity FcεRI receptor. Omalizumab was also associated with significantly greater reductions in eosinophil counts in the airway tissue and sputum, as well as a lower number of cells staining for interleukin (IL)-4.^[12]

Ex vivo evaluation of peripheral eosinophils and T-lymphocyte cytokine profiles from 19 patients with allergic asthma showed a significant increase in binding to Annexin V, a marker of eosinophil apoptosis, among omalizumab recipients when compared with placebo recipients.^[13] Omalizumab was also associated with downregulation of the inflammatory cytokines IL-2 and IL-13.^[13] In addition, these investigators had previously demonstrated that omalizumab reduced blood eosinophils by ≈30% from baseline after 16 and 52 weeks of treatment in patients with allergic asthma, which represented a significant decrease in blood eosinophils compared with placebo.^[14]

Although administration of subcutaneous omalizumab does not appear to be associated with improvement in airway hyperresponsiveness to methacholine in patients with allergic asthma,^[12,15] it has been shown to reduce airway responsiveness to adenosine 5' monophosphate (AMP),^[15] suggesting that there is a stronger link between IgE and the development of AMP- than methacholine-induced bronchoconstriction in this patient population.^[15]

3. Pharmacokinetic Properties

Limited data are available on the pharmacokinetic properties of omalizumab following subcutaneous administration in patients with allergic asthma. This section highlights data from the EU summary of product characteristics^[4] and the US prescribing information^[5] on the pharmacokinetics of subcutaneous omalizumab in adults and adolescent patients with allergic asthma. Mechanism-based pharmacokinetic/pharmacodynamic models of the pharmacokinetics of omalizumab and its binding to IgE have also been published,^[16,17] although a discussion of these papers is beyond the scope of the current review.

The mean absolute bioavailability of subcutaneously administered omalizumab is 62%, and the drug is absorbed slowly, achieving peak serum concentrations after a mean of 7–8 days following single-dose administration.^[4,5] At doses >0.5 mg/kg, the pharmacokinetics of omalizumab are linear. Values at steady state for omalizumab area under the concentration-time curve (AUC)

from day 0 to day 14 were up to 6-fold higher than those calculated following the first dose. The apparent volume of distribution of omalizumab is 78 ± 32 mL/kg (mean value $\pm$ standard deviation).

Omalizumab has a mean elimination half-life of 26 days in sera of asthmatic patients.^[4,5] Apparent clearance is 2.4 ± 1.1 mL/kg/day, although doubling of bodyweight approximately doubles apparent clearance of omalizumab. IgG clearance processes and specific binding and complex formation with IgE are involved in omalizumab clearance; IgG is eliminated by the liver and in bile.

Population pharmacokinetic data suggest that dosage adjustments of omalizumab in adolescent and adult patients are not necessary on the basis of age (12–76 years), race, ethnicity or gender.^[4] Pharmacokinetic data on omalizumab in patients with renal or hepatic impairment are not available.^[4]

Although formal drug interaction studies have not been conducted with omalizumab,^[5] potential interactions between omalizumab and commonly prescribed medication for asthma appear to be unlikely because cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of omalizumab.^[4]

4. Therapeutic Efficacy

The therapeutic efficacy of subcutaneous omalizumab as add-on therapy with ICS-based treatment has been evaluated in several clinical trials, including the INNOVATE (Investigation of Omalizumab in Severe Asthma Treatment) study in patients with severe persistent allergic asthma (section 4.1),^[18] three randomized, double-blind studies^[8,9,19] and a randomized, open-label trial^[20] in patients with moderate to severe allergic asthma (section 4.2), and the SOLAR (Study of Omalizumab in Comorbid Asthma and Rhinitis) trial in patients with concomitant allergic asthma and allergic rhinitis (section 4.3).^[21]

The following subsections highlight data from these fully published papers evaluating omalizumab in adults and adolescents (aged ≥ 12 years); contributory data from abstract reports are included where appropriate (and are clearly identified as abstracts when discussed). In addition, extensions, subgroup analyses, and pooled analyses of some of the key trials have been reported separately and are included in the appropriate subsections. Although omalizumab has also been evaluated in pediatric patients,^[22,23] the drug is not currently approved for use in children under 12 years of age,^[4,5] and inclusion of these data is beyond the scope of this review. Similarly, data from an early pivotal trial^[24] with omalizumab are excluded because the drug was administered intravenously, which is not an approved route of administration for omalizumab.

Clinical trials with omalizumab used a subcutaneous dosage regimen of ≥ 0.016 mg/kg/IgE (IU/mL) per 4 weeks, with the specific dosage and frequency of administration depending on bodyweight and pretreatment serum total IgE levels. Therefore, patients typically received omalizumab 150 or 300 mg every 4 weeks, or 225, 300, or 375 mg every 2 weeks. These are the approved dosage regimens for subcutaneous omalizumab in the EU and the US,^[4,5] although EU labeling also allows a regimen of 75 mg every 2 weeks for certain patients.^[4] Patients enrolled in the clinical trials with omalizumab had serum total IgE levels of ≥ 30 to ≤ 700 IU/mL, which is also in agreement with both EU and US prescribing information (section 7). The only exception was the SOLAR trial in patients with concomitant allergic asthma and persistent allergic rhinitis (section 4.3), in which an IgE level ≥ 30 to ≤ 1300 IU/mL was allowed.^[21] Other important inclusion criteria for the clinical trials with omalizumab are specified in the following subsections.

4.1 INNOVATE Study in Patients with Severe Persistent Allergic Asthma

The INNOVATE study^[18] was a randomized, double-blind, placebo-controlled, multicenter trial in adult and adolescent patients (12–75 years of age) with severe persistent asthma whose symptoms were inadequately controlled despite Global Initiative for Asthma (GINA) 2002 step 4 therapy, which comprised high doses of ICS (>1000 μ g/day of beclomethasone dipropionate or equivalent) plus a long-acting β_2 -agonist and additional controller medication if needed. Patients were also required to have a positive skin prick test, a forced expiratory volume in 1 second (FEV₁) of ≥ 40 to $<80\%$ of predicted normal value, and exacerbations of asthma during the past year that required systemic corticosteroids. Additional inclusion criteria were also specified to ensure that the most severely affected patients were enrolled in the trial.^[18] Although 482 patients were randomized to receive 28 weeks of treatment with omalizumab or placebo, the primary efficacy analysis was conducted in 419 patients (87%) who were randomized after a protocol amendment was introduced to reflect changes to the GINA guidelines, which had been updated in 2003. Thus, the primary intent-to-treat (PITT) population comprised the 419 patients who were randomized after the protocol amendment to receive omalizumab ($n = 209$) or placebo ($n = 210$), although an analysis of the entire intent-to-treat (ITT) population of 482 patients was also reported. The larger ITT population was used for the analysis of safety and tolerability (section 5).

The primary efficacy endpoint was the rate of clinically significant asthma exacerbations during the 28-week double-blind treatment phase.^[18] This was defined as a worsening of asthma symp-

toms requiring treatment with systemic corticosteroids. However, a difference between groups was noted in asthma exacerbation history during the previous year, and the unexpected discrepancy continued during an 8-week run-in phase prior to randomization. A *post hoc* adjustment was therefore made to the primary endpoint analysis to factor in differences in pretreatment exacerbation rates. The 8-week run-in phase included a 4-week period in which each patient's asthma therapy was reviewed and could be adjusted, and advice was provided on allergen avoidance and inhaler technique, followed by a 4-week period during which no further adjustments in asthma therapy were allowed.^[18] An overview of the main findings from the INNOVATE trial and subgroup analyses is presented in table I.

In addition to ICS and long-acting β_2 -agonist therapy, a proportion of patients in the omalizumab group were receiving antileukotrienes (35%), theophylline or related compounds (31%), and maintenance oral corticosteroids (23%) at baseline.^[18] Mean dosage of ICS (beclomethasone dipropionate equivalent) was 2359 μ g/day, mean FEV₁ was 61% of predicted, mean rescue medication use was 6.6 puffs/day and mean serum total IgE level at baseline was 198 IU/mL in the omalizumab group. Mean age was 43.4 years and mean duration of allergic asthma was 23.3 years. All of these parameters were generally similar between omalizumab and placebo recipients.

Results of the primary efficacy analysis in the PITT population, after adjustment for pretreatment exacerbation history, showed that the rate of clinically significant asthma exacerbation during the 28-week treatment period was 0.68 (95% CI 0.53, 0.87) in the omalizumab group compared with 0.91 (95% CI 0.73, 1.14) among placebo recipients ($p = 0.042$), which represents a relative reduction of 26%.^[18] A statistically significant difference favoring omalizumab over placebo was also observed for the rate of severe asthma exacerbation (0.24 [95% CI 0.17, 0.35] vs 0.48 [95% CI 0.36, 0.64]; $p = 0.002$), which was defined as peak expiratory flow (PEF) or FEV₁ $<60\%$ of personal best. This represents a 50% relative reduction in the rate of severe asthma exacerbations.

Omalizumab was also associated with significant reductions compared with placebo in the rate of emergency room visits for asthma (0.24 vs 0.43; $p = 0.038$), and significantly greater improvements in total asthma score (specific values not reported; $p = 0.039$), mean morning PEF (specific values not reported; $p = 0.042$), and FEV₁ (% predicted) [improvements were 190 vs 96 mL; $p = 0.043$].^[18] Although the difference between groups was not statistically different for rescue medication use, omalizumab-treated patients used ≈ 0.5 puffs/day less than placebo recipients.

Asthma-related quality of life (QOL), as assessed using the Asthma Quality of Life Questionnaire (AQLQ), was significantly improved with omalizumab compared with placebo overall (least

Table I. Overview of main findings from the INNOVATE (Investigation of Omalizumab in Severe Asthma Treatment) study and various subgroup analyses. INNOVATE was a randomized, double-blind, 28-week trial comparing omalizumab and placebo as add-on therapy in patients (pts) with severe allergic asthma. For all comparisons shown, there was a statistically significant difference between groups^a

Study population or subgroup	Main results (omalizumab vs placebo)
Overall group of 419 pts ^{[18] b}	26% reduction ^c in the rate of clinically significant asthma exacerbations (primary endpoint); 50% reduction ^c in rate of severe asthma exacerbations
Subgroup of pts requiring oral corticosteroids at baseline (n = 91) ^{[25] d}	37% reduction in clinically significant asthma exacerbations
Subgroup of pts treated with inhaled fluticasone/salmeterol ^e 500 µg/50 µg bid (n = 80) ^{[26,27] d}	Improvements in FEV ₁ ^[26] and AQLQ scores ^[27]
Subgroup of pts treated with inhaled fluticasone/salmeterol ^e (dosage not specified) [n = 159] ^{[28] d}	37% reduction in the need for rescue bursts of systemic corticosteroids

a p < 0.05 or upper bound of the 95% CI for relative risk was not >1.00.

b Primary intent-to-treat population who were randomized after a protocol amendment.

c After adjustment for asthma exacerbation history.

d Reported as abstract(s).

e Fixed-dose combination.

AQLQ = Adult Asthma Quality of Life Questionnaire; **bid** = twice daily; **FEV₁** = forced expiratory volume in 1 second.

squares mean difference 0.45; $p < 0.001$) and across all domains of the instrument.^[18] Moreover, significantly more patients in the omalizumab group than in the placebo group had improvements from baseline of ≥ 0.5 (60.8% vs 47.8%; $p = 0.008$), ≥ 1.0 (45.1% vs 24.9%; $p < 0.001$), or ≥ 1.5 (27.5% vs 17.1%; $p = 0.011$) in AQLQ scores, reflecting clinically significant improvements that were small, moderate or large in magnitude. In addition, both physician and patient global evaluations of treatment effectiveness significantly ($p < 0.001$) favored omalizumab over placebo. Omalizumab treatment was rated as excellent or good in 60.5% and 64.3% of patients when assessed by investigators and patients, respectively. In contrast, placebo was rated as excellent or good in $\approx 43\%$ of patients, whether assessed by clinicians or by patients.^[18]

4.1.1 Subgroup Analyses of the INNOVATE Study

A number of subgroup analyses of the INNOVATE study have been conducted, all of which are available as abstracts.^[25-31] One such analysis included 91 patients who required oral corticosteroids at baseline.^[25] Compared with placebo recipients, patients treated with omalizumab had statistically significant reductions in total asthma symptom score ($p = 0.012$; specific scores not reported) as well as a 37% reduction in the rate of clinically significant asthma exacerbation (0.80 vs 1.26; $p = 0.111$). The absolute difference between treatment groups (0.46 vs 0.21; statistical analysis not reported) was approximately double that of the larger subgroup not receiving oral corticosteroids at baseline, suggesting that omalizumab has greater efficacy in patients with more severe disease.

Several analyses were conducted by Massanari and colleagues in patients who received ICS therapy specifically with fluticasone/salmeterol 500 µg/50 µg twice daily in a fixed-dose combination ($n = 80$)^[26,27] or with fluticasone/salmeterol in a fixed-dose combination, but without a specified dosage regimen ($n = 159$).^[28] Results of these analyses showed that omalizumab significantly improved FEV₁ compared with placebo (mean improvement 269 mL vs 28 mL; $p = 0.003$),^[26] and was associated with significantly improved AQLQ scores (least squares mean difference between omalizumab and placebo recipients 0.60; 95% CI 0.08, 1.12; $p = 0.024$)^[27] and a reduced need for rescue bursts of systemic corticosteroids (relative risk 0.63; 95% CI 0.39, 1.00).^[28] The same investigators also showed that, compared with placebo, omalizumab reduced the rate of clinically significant asthma exacerbations by 32% (rate ratio 0.676; 95% CI 0.363, 1.257) among patients who were enrolled in the INNOVATE study after hospitalization (or prolonged emergency room visit) for severe asthma exacerbation.^[29]

Other subgroup analyses have shown a good correlation between the gradual decline in serum omalizumab concentrations and worsening asthma control after discontinuation of the drug in 118 patients deemed by their physicians to be responders to omalizumab therapy during the active treatment phase.^[30] In addition, after 26–28 weeks of therapy, the percentage of symptom-free days per patient was numerically higher among omalizumab responders than in the overall group of omalizumab recipients (46% vs 37%).^[31]

4.2 Randomized Studies in Patients with Moderate to Severe Allergic Asthma

Randomized trials with omalizumab in adults and adolescents with moderate to severe allergic asthma have been previously reviewed in some detail,^[6,32] and this section provides an overview of these data, focussing on results from three randomized, double-blind trials^[8,9,19] and a randomized, open-label (naturalistic) study.^[20] Extensions^[33,34] of the two largest double-blind, randomized trials^[8,9] are also fully published, and abstract reports are available providing results from an extension^[35] of the smaller randomized, double-blind trial^[19] and an extension^[36] of the randomized, open-label trial.^[20] A recent subgroup analysis of the open-label trial has also been conducted (available as an abstract report).^[37]

The randomized, double-blind studies were of 28^[8,9] or 32^[19] weeks' duration, including an initial 16-week period during which ICS doses remained stable (stable-corticosteroid [SCS] phase), followed by a 12- or 16-week period in which ICS doses were tapered (corticosteroid-reduction [CSR] phase). In the two largest trials ($n = 525$;^[9] $n = 546$ ^[8]), patients were switched from their current dose of ICS to an equivalent dose of inhaled beclomethasone dipropionate during a 4- to 6-week run-in period. These studies shared most of the same inclusion criteria, such as a positive skin prick test, an FEV₁ of ≥ 40 to $\leq 80\%$ of predicted normal value, FEV₁ reversibility of $\geq 12\%$ within 30 minutes after administration of salbutamol (albuterol), and current treatment with an ICS (although specified dosage range differed between studies).^[8,9] In the other randomized, double-blind trial ($n = 246$),^[19] the main inclusion criteria were that patients had severe allergic asthma (not defined) and required ≥ 1000 $\mu\text{g/day}$ of inhaled fluticasone; all patients were switched to an equivalent dose of inhaled fluticasone during a 6- to 10-week run-in period.

The primary endpoint of the two larger trials was the number of asthma exacerbations experienced during treatment (defined as requiring systemic corticosteroids or double the baseline beclomethasone dipropionate dosage).^[8,9] In the smallest of the three double-blind, randomized trials, the primary endpoint was the percentage reduction from baseline in inhaled fluticasone dose.^[19]

The two largest randomized trials included patients with similar baseline characteristics, and omalizumab and placebo recipients were well matched.^[8,9] Mean ranges of baseline values for all randomized patients in these two trials were as follows: age 39.0–40.0 years; duration of asthma 19.1–22.7 years; inhaled beclomethasone dipropionate dose 568–772 $\mu\text{g/day}$; FEV₁ 67.7–69.9% of predicted; serum total IgE level 172.5–223.1 IU/mL. These values were broadly similar to those for patients included in the smaller randomized trial,^[19] although mean IgE

level was numerically higher (267 IU/mL among omalizumab recipients) and mean FEV₁ lower (62.9% of predicted) than in the larger studies. In addition, the mean inhaled fluticasone dose was 1375 $\mu\text{g/day}$, and 49% of omalizumab recipients were receiving long-acting β_2 -agonists at baseline.^[19]

The randomized, open-label trial included 312 patients with moderate to severe asthma who were receiving best standard care (BSC), including inhaled beclomethasone dipropionate ≥ 400 $\mu\text{g/day}$ (adolescents) or ≥ 800 $\mu\text{g/day}$ (adults) or equivalent dose of ICS.^[20] Patients were randomized to continue to receive BSC with or without omalizumab for 1 year. The primary endpoint of the study was the annualized number of asthma deterioration-related incidents (ADRI), i.e. systemic corticosteroids or antibiotics required for ≥ 2 days, ≥ 2 days of school/work missed, unscheduled physician visit, hospitalization or emergency room visit. Baseline characteristics (median values) for omalizumab recipients were as follows: age 37.5 years; inhaled beclomethasone dipropionate dosage 2000 $\mu\text{g/day}$; total serum IgE level 167 IU/mL; FEV₁ 70.5% of predicted; receiving systemic corticosteroids 22.8%; and receiving long-acting β_2 -agonists 77.7%. In general, patients in the omalizumab group were well matched with those in the group receiving BSC alone.

4.2.1 Effect on Asthma Exacerbations

Compared with placebo, omalizumab was associated with relative reductions of 41–58% in the mean number of asthma exacerbations (primary endpoint) in the two larger double-blind, randomized trials of 28 weeks' duration (figure 1).^[8,9] Reductions were 48%^[9] and 58%^[8] in the 16-week SCS phase, and 41%^[9] and 52%^[8] in the 12-week CSR phase. For all comparisons, the difference between treatment groups was statistically significant.

These reductions in asthma exacerbation rates were achieved despite greater reductions in ICS dosages among omalizumab than placebo recipients during the CSR phase of the trials (section 4.2.3).^[8,9] One of the studies^[9] also reported a significantly shorter mean duration of exacerbations during both the SCS phase (7.8 vs 12.7 days; $p < 0.001$) and the CSR phase (9.4 vs 12.6 days; $p = 0.021$) in the omalizumab group compared with the placebo group. During a 24-week extension of this trial which included 460 patients,^[34] significantly fewer omalizumab than placebo recipients experienced ≥ 1 acute asthma exacerbation (31.8% vs 42.8%; $p = 0.015$). Similar results were reported in a 24-week extension ($n = 483$)^[33] of the other large trial (24% vs 41%; $p < 0.001$). In addition, both extension studies showed that the mean number of exacerbations per patient was significantly reduced by omalizumab compared with placebo (0.60 vs 0.83 [$p = 0.023$] in one trial^[34] and 0.48 vs 1.14 [$p < 0.001$] in the other study^[33]).

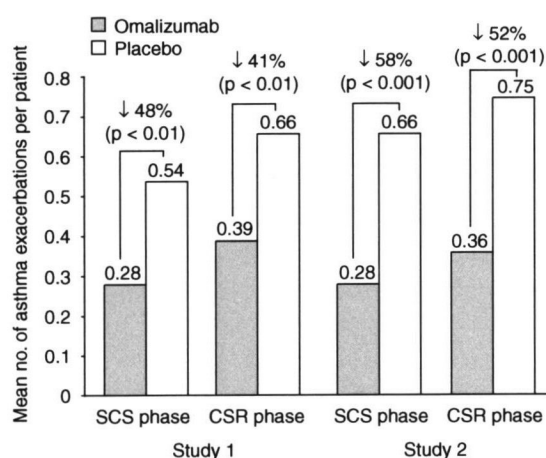


Fig. 1. Asthma exacerbation rates in two large randomized, double-blind trials comparing subcutaneous omalizumab and placebo in patients with moderate to severe allergic asthma.^[8,9] The 28-week studies comprised a 16-week stable-corticosteroid (SCS) phase and a 12-week corticosteroid-reduction (CSR) phase. The rate of asthma exacerbation (defined as requiring systemic corticosteroids or double the baseline beclomethasone dipropionate dosage) was the primary endpoint of both trials. Study 1^[9] included 525 patients and Study 2^[8] included 546 patients. ↓ indicates decrease.

Results of the smaller randomized, double-blind trial in patients with relatively severe allergic asthma (mean FEV₁ ≈ 64% predicted) showed that omalizumab recipients had a 35–45% lower rate of asthma exacerbation than placebo recipients, although the difference between treatment groups did not achieve statistical significance for this secondary endpoint.^[19] The mean numbers of exacerbation episodes per patient for the omalizumab and placebo groups were 0.15 and 0.23 during the SCS phase, and 0.19 and 0.34 in the CSR phase.

In the open-label, randomized trial, omalizumab (plus BSC) was associated with a relative reduction of 60.8% (95% CI 46.9,

71.0) in the mean number of clinically significant asthma exacerbations per patient-year (1.12 vs 2.86; $p < 0.001$) compared with BSC only.^[20] There were also significantly more patients in the omalizumab than in the BSC group who remained exacerbation-free during the study period (49.5% vs 26.4%; $p = 0.001$). The proportion of patients with ≥2 exacerbations was also reduced by about half with omalizumab (20.4% vs 42.5%; $p = 0.001$). Sub-group analysis of 164 patients with severe disease, despite high-dose ICS plus a long-acting β-agonist, showed a 59% relative reduction in the annual rate of asthma exacerbations with omalizumab compared with BSC (1.26 vs 3.06; $p < 0.001$).^[37] In addition, omalizumab provided good or excellent control of asthma symptoms in 53 of 57 patients (93%) who were treated with the drug for up to 4 years in long-term extensions of the open-label trial (reported as an abstract).^[36]

4.2.2 Effect on Asthma Symptoms, Rescue Medication Use and Pulmonary Function

Asthma symptom scores were significantly improved and rescue medication use with inhaled salbutamol (albuterol) was significantly reduced among omalizumab recipients compared with patients in the placebo or BSC groups of the randomized trials.^[8,9,19,20]

Results from the two largest randomized, double-blind trials comparing omalizumab and placebo in patients with moderate to severe allergic asthma are presented in table II. In one trial, mean total asthma scores were reduced by omalizumab from a baseline value of 4.31 to a score of 2.51 at the end of the SCS phase and 2.36 at the end of the CSR phase.^[9] Reductions at the end of the SCS and CSR phases were significantly greater than those reported with placebo (table II), and a significant difference favoring omalizumab over placebo ($p < 0.001$) was noted as early as

Table II. Secondary outcomes from the two largest randomized, double-blind trials with omalizumab in patients (pts) with moderate to severe allergic asthma.^[8,9] All patients were also treated with inhaled corticosteroids (ICSs). Studies were 28 weeks in duration, including a 16-week stable-corticosteroid (SCS) phase followed by a 12-week corticosteroid-reduction (CSR) phase

Study	Treatment (no. of pts)	Reduction from baseline in mean ^[9] or median ^[8] total asthma symptom score ^{a,b}		Reduction from baseline in rescue medication use (no. of puffs/day) ^{a,c}		Reduction from baseline in ICS use	
		end of SCS phase	end of CSR phase	end of SCS phase	end of CSR phase	median dosage reduction (%)	pts with ≥50% reduction (%)
Busse et al. ^[9]	Omalizumab (268)	1.80**	1.95**	1.5*	1.6**	75***	72.4***
	Placebo (257)	1.27	1.45	1.0	1.0	50	54.9
Solèr et al. ^[8]	Omalizumab (274)	1.4***	1.6**	2.0***	2.2***	80*** ^a	79
	Placebo (272)	0.9	1.3	0.4	1.2	47 ^a	55

a Values estimated from a graph.

b Baseline values 3.9–4.31.

c Baseline use of salbutamol (albuterol) 4.0–4.9 puffs/day.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs placebo.

week 4. The use of rescue medication among omalizumab recipients was 4.9 puffs/day at baseline, which was reduced to 3.4 and 3.3 puffs/day at the end of the SCS and CSR phases, respectively. These reductions were significantly greater than those observed in the placebo group (table II), and significant differences between groups were noted by week 4 ($p < 0.05$).^[9] Similar results were also observed in the other large study, with statistical differences favoring omalizumab at the end of the SCS and CSR phases for reductions in total asthma score and rescue medication use (table II).^[8] Significant between-group differences were noted as early as week 4 for total asthma score ($p \leq 0.001$) and rescue medication use ($p < 0.005$).

Omalizumab was also associated with statistically significant improvements in asthma symptom scores and rescue medication use at most or all timepoints compared with placebo in the smallest of the three randomized, double-blind studies.^[19] Changes from baseline to the end of the randomized, open-label trial also favored omalizumab over BSC for these parameters.^[20] At the end of the study, omalizumab-treated patients required a median of 0.60 puffs of rescue medication per day compared with 3.00 puffs per day for patients in the BSC group ($p < 0.001$). The improvement in asthma symptom scores from baseline to the end of the study was also significantly greater with omalizumab than BSC (6.2 vs 0.7; $p < 0.001$).

The primary outcome of the randomized, open-label trial was the composite ADRI endpoint, and omalizumab reduced ADRI per patient-year by 49.6% (95% CI 27.8, 64.8) compared with BSC.^[20] On average, patients had 4.84 fewer events (ADRI) per patient-year if they received omalizumab. When omalizumab was compared with BSC in the subgroup of 164 patients with severe allergic asthma, despite high-dose ICS plus a long-acting β -agonist, ADRI were also reduced by 40% (5.61 vs 9.40; $p < 0.05$).^[37]

In all of the randomized trials, omalizumab was associated with statistically significantly greater improvements from baseline in FEV₁ than placebo^[8,9,19] or BSC^[20] at various timepoints. In addition, FEV₁ remained stable and >80% of patients had good or excellent control of symptoms during a 3-year extension ($n = 178$) of the smaller, 32-week, randomized, double-blind trial [reported as an abstract].^[35] Omalizumab was also associated with significantly greater increases in morning PEF values in some studies.^[8,9] However, these results should be interpreted with caution because the absolute improvements in lung function reported with omalizumab were relatively small and may not have been clinically meaningful.

4.2.3 Corticosteroid Dose Reduction

Median ICS dose reductions were 75%^[9] and 80%^[8] among omalizumab recipients during the 12-week CSR phase of the two

largest randomized, double-blind trials in patients with moderate to severe allergic asthma (table II). In both studies, the dose reductions were significantly ($p < 0.001$) greater than those achieved among placebo recipients.^[8,9] One trial^[9] also showed a significantly higher proportion of patients in the omalizumab group than in the placebo group who had ICS dose reduction $\geq 50\%$ (72.4% vs 54.9%; $p < 0.001$) or complete ICS withdrawal (39.6% vs 19.1%; $p < 0.001$). Although results were of a similar magnitude in the other large trial, between-group differences did not achieve statistical significance for these outcomes.^[8] However, during 24-week double-blind extensions of both studies (total treatment period 52 weeks), patients in the omalizumab group had a sustained, significant ($p < 0.001$) reduction in mean ICS dose compared with placebo.^[33,34]

The primary endpoint of the smallest of the three randomized, double-blind trials was the percentage reduction from baseline in inhaled fluticasone dose after 32 weeks of treatment.^[19] Fluticasone dose was reduced to a significantly greater extent with omalizumab than with placebo (mean reduction 57.2% vs 43.3%; $p = 0.003$). Almost three-quarters of omalizumab recipients had a fluticasone dose reduction $\geq 50\%$ compared with just over half of placebo recipients (74% vs 51%; $p = 0.001$). During a 3-year extension of the trial, there was an 11% reduction in ICS use among patients who were receiving ICS at the beginning of the extension period [reported as an abstract].^[35]

There was also a significant ($p < 0.001$) between-group difference favoring omalizumab over BSC for change from baseline in ICS dose in the randomized, open-label study.^[20]

4.2.4 Effect on Asthma-Related Quality of Life

The effect of omalizumab on asthma-related QOL was assessed using the 32-item AQLQ instrument in the randomized, double-blind studies in patients with moderate to severe allergic asthma.^[8,9,19] For the two largest trials, asthma-related QOL results were reported separately from the clinical results, with effects measured at weeks 16 (end of the SCS phase), 28 (end of the CSR phase) and 52.^[38,39]

In both of the larger studies, the mean improvement from baseline in overall AQLQ score was significantly greater ($p < 0.01$) among omalizumab than placebo recipients at the end of the SCS phase (0.88^[39] and 0.93^[38] with omalizumab vs 0.60 and 0.66 with placebo) and at the end of the CSR phase (1.05^[39] and 0.97^[38] with omalizumab vs 0.66 and 0.70 with placebo) [some values estimated from a graph]. Compared with placebo, omalizumab was associated with statistically significant improvements in all four AQLQ domains (emotional functioning, activity limitations, asthma symptoms and environmentally induced symptoms) at all three follow-up periods in both studies,^[38,39] except environ-

mental exposure score at week 16 in one study.^[39] Both studies also showed that omalizumab recipients were more likely to achieve clinically meaningful improvements in AQLQ scores (≥ 0.5 points) than placebo recipients during each phase of the study.^[38,39]

The effects of omalizumab on asthma-related QOL were also compared with placebo in the smallest of the three randomized, double-blind trials.^[19] Clinically meaningful improvements in overall AQLQ scores (≥ 0.5 points) were reported in 58% of patients treated with omalizumab compared with 39% of those who received placebo ($p < 0.01$), and similar differences between treatment groups were observed across the four AQLQ domains.

Global evaluation of the effectiveness was also evaluated in one of the large, randomized trials.^[9] A total of 61% of omalizumab recipients rated omalizumab as good or excellent compared with 38% of those who received placebo ($p < 0.001$). Physician-rated assessment also favored omalizumab (53% vs 33%; $p < 0.001$).

4.2.5 Results of Pooled Analyses

Several fully published pooled analyses of phase III clinical trials in patients with moderate to severe allergic asthma have assessed the efficacy of omalizumab on various outcomes.^[40-43] Most^[43] or all^[40-42] patients included in these retrospective analyses were aged ≥ 12 years. Although there were some differences between the pooled analyses in terms of which studies were included, most used results of the randomized trials discussed earlier in section 4.2, along with those from the INNOVATE study in patients with severe persistent disease (section 4.1), and the SOLAR trial in patients with concomitant allergic asthma and allergic rhinitis (section 4.3). In addition, all but one^[43] of the analyses reported that the vast majority ($>90\%$) of patients met the criteria for the GINA (2002) classification of severe persistent asthma.^[40-42] Numerous other pooled analyses evaluating clinical outcomes with omalizumab are available as abstract reports, and a Cochrane review^[32] on omalizumab in chronic asthma is also available; however, discussion is limited to the fully published analyses.

In general, results of the pooled analyses support and strengthen the findings of the individual trials. Two analyses included the same seven randomized trials ($n = 4308$) but reported on different outcomes.^[40,41] Compared with current asthma therapy (control), the addition of omalizumab significantly reduced the need for systemic corticosteroid bursts (relative risk 0.57 [95% CI 0.48, 0.66]; $p < 0.001$), and was associated with a significantly higher rate of response (complete or marked improvement in symptom control) according to physician's overall assessments (58.5% vs 36.9%; $p < 0.001$) and patient's overall assessments (64.2% vs 43.9%; $p < 0.001$).^[41] The rates of asthma exacerbation and

emergency room visits were also significantly ($p < 0.0001$) reduced by 38% and 47%, respectively, among omalizumab recipients compared with the control group.^[40]

Two other analyses focused on asthma-related QOL outcomes ($n = 2548$ ^[42]; $n = 2056$ ^[43]). In one analysis, patients in the omalizumab group had a higher mean increase from baseline to endpoint in overall AQLQ score compared with placebo (1.01 vs 0.61; $p < 0.001$), and clinically meaningful improvements (≥ 0.5 point) were achieved in 66.3% and 52.4% of patients in the respective groups ($p < 0.001$).^[42] The other analysis showed that, compared with placebo, omalizumab was associated with a 1.6- to 2.0-fold increase in moderate (≥ 1 point) and a 1.8- to 2.1-fold increase in large (≥ 1.5 point) improvements in overall AQLQ scores.^[43]

4.3 SOLAR Study in Patients with Concomitant Allergic Asthma and Allergic Rhinitis

The randomized, double-blind, multicenter SOLAR study evaluated the clinical efficacy of omalizumab in adult and adolescent patients with concomitant moderate to severe allergic asthma and persistent allergic rhinitis.^[21] Patients receiving a stable dose of ICS and who had a specified number of unscheduled medical visits for asthma over the previous year or two were randomized to receive omalizumab ($n = 209$) or placebo ($n = 196$) for 28 weeks. The co-primary endpoints of the trial were the incidence of asthma exacerbations and the proportion of patients with improvement (≥ 1 point) in both asthma- and rhinitis-related QOL scores, as assessed by the AQLQ and the Rhinitis Quality of Life Questionnaire (RQLQ). Asthma exacerbation was defined as worsening of asthma requiring treatment with systemic corticosteroids or doubling the baseline dose of ICS.

The ITT population comprised all 405 patients who were randomized, and the per-protocol population comprised 366 patients who completed the study without major protocol deviations.^[21] The proportion of patients with at least one asthma exacerbation during the study period was significantly lower among omalizumab than placebo recipients in the ITT (20.6% vs 30.1%; $p = 0.02$) and per-protocol (18.8% vs 28.2%; $p = 0.0225$) populations. There was also a significantly greater proportion of patients in the omalizumab group than in the placebo group who had an improvement of ≥ 1 point in both AQLQ and RQLQ scores (57.7% vs 40.6%; $p < 0.001$). The latter analysis included a total of 400 patients. Compared with placebo, omalizumab was associated with significantly greater improvements in overall AQLQ ($p < 0.05$) and overall RQLQ ($p < 0.001$) scores, as well as all RQLQ domain scores and two of the four AQLQ domain scores. Various secondary outcomes were also significantly improved

with omalizumab compared with placebo, including Wasserfallen asthma and rhinitis clinical symptom scores, and patient's and physician's assessments of treatment effectiveness. Additional findings from the SOLAR study (reported separately as an abstract)^[44] indicate that patients whose asthma responds to omalizumab are several-fold more likely to experience improved control of rhinitis symptoms than those who were deemed to be asthma nonresponders to omalizumab therapy.

5. Tolerability

In general, subcutaneous administration of omalizumab in adult and adolescent patients with moderate to severe allergic asthma was well tolerated in the clinical trials discussed in section 4.^[8,9,18-21] Most adverse events were mild or moderate in severity and were reported with a frequency that did not differ from those in placebo or control groups.

The most common adverse events with omalizumab are injection-site reactions (e.g. injection site pain, bruising, swelling, erythema, and pruritus),^[4,5] and these were reported in 45% of omalizumab recipients compared with 43% of placebo recipients in clinical trials.^[5] Severe injection site reactions were reported in 12% and 9% of patients, respectively. Other frequently reported adverse events with omalizumab in clinical trials included viral infection (23%), upper respiratory tract infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%), although these were reported with similar frequency among placebo recipients.^[5]

Tolerability data from the INNOVATE study^[18] in patients with severe allergic asthma were broadly similar to those from other clinical trials evaluating omalizumab in patients with moderate to severe disease. Most adverse events were mild or moderate in severity. The overall incidence of adverse events was 72.2% among omalizumab recipients compared with 75.5% among placebo recipients. The incidence of adverse events related to study medication was 11.8% and 9.3% in the omalizumab and placebo groups. The incidence of serious adverse events was 11.8% among omalizumab recipients and 15.6% among placebo recipients, and the total incidence of injection site reactions was 5.3% and 1.3% in the respective treatment groups.^[18]

Anaphylaxis and malignancies are the most serious events reported in clinical trials with omalizumab.^[4,5,45] Although the incidence of malignant neoplasms was numerically higher among patients receiving omalizumab than those in control groups (0.5% vs 0.2%), the overall incidence for omalizumab-treated patients was similar to that reported in the general population.^[4,45] Moreover, in view of the wide range of cancer types observed, along with the relatively short duration of exposure to omalizumab (<1

year) and the clinical features of the individual cases, a causal relationship appears to be unlikely.^[4,45]

Anaphylaxis occurred rarely in clinical trials with omalizumab,^[4,5] but has also been reported in postmarketing surveillance data, such that estimates for the incidence of anaphylaxis with omalizumab range from ≈ 0.1 –0.2%.^[5,46] US prescribing information states that the incidence of anaphylaxis is at least 0.2% and is based on data from 57 300 patients treated with omalizumab between June 2003 and December 2006;^[5] however, it is unclear what criteria were used to define anaphylaxis.^[46] Therefore, a joint task force was formed from the executive committees of the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) to review the clinical trial and postmarketing surveillance data on anaphylaxis.^[46] The joint task force of the AAAAI/ACAAI determined that 35 patients experienced a total of 41 episodes of clearly defined anaphylaxis during the same period of time in which 39 510 patients received omalizumab, which corresponds to an anaphylaxis reporting rate of 0.09% of patients. All patients responded to treatment for anaphylaxis and no patient required intubation.^[46] Although most of these reactions occurred within 2 hours of administration of the first or subsequent injections of omalizumab, anaphylaxis has occurred >24 hours after an injection and >1 year after beginning regularly scheduled treatment.^[4,5,45] As a precaution, the joint task force of the AAAAI/ACAAI recommend direct observation for 2 hours after the first three omalizumab treatments and for 30 minutes after subsequent omalizumab treatments.^[46] A boxed warning regarding anaphylaxis appears in US prescribing information for omalizumab.^[5]

Omalizumab does not appear to be associated with clinically significant laboratory abnormalities (liver function tests, serum creatinine levels, urinalysis or haematology).^[45] In rare instances, patients may develop antibodies to omalizumab.^[4] Serum total IgE levels increase during omalizumab treatment (due to omalizumab:IgE complex formation) and may persist for up to 1 year after discontinuation of therapy.^[5] Serum total IgE levels should not be used to reassess omalizumab dosage requirements if blood samples are obtained <1 year following discontinuation of the drug.

6. Pharmacoeconomic Considerations

A full discussion of the pharmacoeconomics of omalizumab in allergic asthma is beyond the scope of this article, but in view of the high acquisition cost of omalizumab (>\$US1000 per patient per month^[47]), a brief overview of fully published cost-effectiveness (or cost-utility) analyses is warranted. A more comprehensive

Table III. Summary of fully published cost-effectiveness analyses with omalizumab in moderate to severe allergic asthma. All analyses included direct costs only, applied appropriate discounting (where applicable^a) and used sensitivity analyses to provide a plausible range of results

Study	Country (year of costing)	Key clinical trial(s) [disease severity]	ICER ^b	Comments
Brown et al. ^[50]	Canada ^c (NR)	One randomized, open-label trial ^[20] [severe disease] ^d	€31 209 per QALY gained	Analysis used a Markov model with a lifetime time horizon, but assumed that patients received omalizumab for 5 years. Most outcomes and resource-use data were derived from the subset of patients with severe disease in the randomized, open-label trial, ^[20] although additional data from the INNOVATE trial ^[18] were also used. The study perspective was not stated
Dewilde et al. ^[51]	Sweden (NR)	INNOVATE ^[18] [severe disease]	€56 091 per QALY gained	Analysis conducted from a societal perspective ^e using a Markov model with a lifetime time horizon. Most outcomes and resource-use data were derived from the INNOVATE trial, with Swedish unit costs applied
Oba and Salzman ^[49]	US (2003)	Two RCTs ^[8,9] [moderate to severe disease]	\$US378 per AQLQ response; \$US523 per additional SCD	Retrospective analysis conducted from a third-party payer's perspective over a time horizon of 1 year. The analysis used pooled data from two studies and focused on cost per AQLQ response (≥0.5-point increase from baseline AQLQ score) or cost per SCD
Wu et al. ^[52]	US (2005)	Various [severe disease]	\$US821 000 per QALY gained	Analysis conducted from a societal perspective ^e using a Markov model and previously published data to project outcomes over a 10-year time horizon

a One analysis used a time horizon of 1 year and, therefore, did not apply discounting to costs or outcomes.^[49]

b ICER values reflect base-case results for the comparison of omalizumab plus ICS-based therapy vs ICS-based therapy.

c Canada was used as the reference country, but costs were expressed in €.

d Although the randomized, open-label trial included patients with moderate to severe disease,^[20] the economic analysis was based on the subgroup of patients who had severe allergic asthma. Where outcomes data for severe disease were not available from the randomized, open-label trial (e.g. severe exacerbations), data from the INNOVATE study^[18] (in patients with severe disease) were used instead.

e Although conducted from a societal perspective, indirect costs, such as those related to time off work due to illness, were not included.

AQLQ = Asthma Quality of Life Questionnaire; **ICER** = incremental cost-effectiveness ratio; **ICSSs** = inhaled corticosteroids; **NR** = not reported; **QALY** = quality-adjusted life-year; **RCT** = randomized, controlled trial; **SCD** = successfully controlled day.

review of the cost effectiveness of omalizumab in allergic asthma is available elsewhere.^[48]

Three of the analyses evaluated the incremental cost per quality-adjusted life-year (QALY) gained for omalizumab plus ICS-based therapy relative to ICS-based therapy in patients with severe allergic asthma (table III).^[50-52] All three analyses used Markov models in which hypothetical cohorts of patients could transition between specific health states, each associated with certain health-care resource use and costs. However, the analyses conducted in Canada^[50] and Sweden^[51] relied primarily on clinical outcomes and resource-use data from a single study (an open-label, naturalistic trial for the Canadian evaluation and the INNOVATE study for the Swedish analysis), whereas the economic analysis conducted in the US^[52] populated the model using a variety of sources to simulate the use of omalizumab in patients with severe allergic asthma. Another notable difference between the analyses is that

the Canadian and Swedish studies used a time horizon of the life-expectancy of patients in the hypothetical cohorts, whereas a 10-year time horizon was used in the US analysis.

Base-case results of the Canadian^[50] and Swedish^[51] analyses calculated incremental cost-effectiveness ratios (ICERs) that were below or close to commonly used ICER thresholds, whereas the US analysis^[52] calculated a highly unfavorable ICER for omalizumab as add-on therapy for severe allergic asthma (table III). In general, ICERs below such thresholds (e.g. \$US50 000–100 000, €50 000 per QALY gained)^[53-55] suggest that the treatment is cost effective, but ICER values above these thresholds suggest the opposite.

The fourth cost-effectiveness analysis,^[49] also conducted in the US, used a short time horizon of 1 year, which was the same time period of the two randomized trials (and extension studies) on which the economic analysis was based (table III). Clinical out-

comes and resource-use data from the two randomized trials were collected retrospectively, and costs for the year 2003 were applied. Results of the base-case analysis showed that the use of omalizumab in patients with moderate to severe allergic asthma was associated with an incremental cost of \$US378 per AQLQ response (≥ 0.5 -point increase from baseline AQLQ score) and \$US523 per additional successfully controlled day. Although there are no generally accepted ICER thresholds for these parameters, results were deemed by the study authors to be unfavorable when compared with similar economic analyses with other agents used in the management of asthma.^[49]

The cost-effectiveness analyses with omalizumab were generally well conducted, in that relevant costs were included, sources of data were clearly stated, clinical outcomes were relevant, appropriate discounting was applied and sensitivity analyses were conducted. However, as with all pharmacoeconomic analyses, there are study limitations. For example, even if the base-case results of cost-effectiveness analyses are robust to reasonable changes in key input variables in sensitivity analyses, they may not be applicable to other geographical regions because of differences in healthcare systems, unit costs and other factors. In addition, modeled analyses project longer-term costs and outcomes from shorter-term clinical trial data, typically using a variety of sources and extrapolating clinical trial results to the general population of interest. The selection of key studies and other data sources used to populate economic models, along with other factors such as the study perspective and specific costs included, can have an important impact on results of these analyses.

7. Dosage and Administration

Omalizumab is available in a number of countries, with some variations between geographical regions in terms of approved indication, dosage and administration guidelines, and monitoring.

In the EU, omalizumab is approved for use as add-on therapy in adult and adolescent patients (≥ 12 years of age) with severe persistent allergic asthma.^[4] Patients must have a positive skin test or *in vitro* reactivity to a perennial aeroallergen, reduced lung function ($FEV_1 < 80\%$), frequent daytime symptoms or night-time awakenings, as well as a history of multiple documented severe asthma exacerbations despite high-dose ICS plus a long-acting inhaled β_2 -agonist. Omalizumab is administered by subcutaneous injection at a dosage of 75–300 mg every 4 weeks or 225–375 mg every 2 weeks. The specific dose and frequency is based on patient bodyweight and pretreatment serum total IgE levels (≥ 30 to ≤ 700 IU/mL) [see EU summary of product characteristics of omalizumab for dosage tables^[4]]. In the EU, patients should be assessed by their physician 16 weeks after initiation of omalizumab therapy

to determine whether a marked improvement in overall asthma control has been achieved, thus warranting further treatment with the drug.

US prescribing information for omalizumab does not mandate a 16-week assessment to determine treatment effectiveness before further injections are administered, although it does state that the need for continued therapy should be periodically reassessed on the basis of disease severity and level of asthma control.^[5] The approved indication in the US, which is broader than that in the EU, is for adults and adolescents (≥ 12 years of age) with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICS. Omalizumab is administered by subcutaneous injection at a dosage of 150–300 mg every 4 weeks or 225–375 mg every 2 weeks. The specific dose and frequency is based on patient bodyweight and pretreatment serum total IgE levels (≥ 30 to ≤ 700 IU/mL) [see US prescribing information for dosage tables^[5]].

In both the EU and the US, omalizumab is available in a single-use vial as sterile, lyophilized powder that takes ≈ 15 –20 minutes to dissolve.^[4,5] The reconstituted solution is viscous and each subcutaneous injection may take 5–10 seconds to administer. Omalizumab doses > 150 mg should be split into multiple injections (i.e. two or three delivery sites, depending on the dose).

Anaphylaxis can occur in patients treated with omalizumab (section 5). US prescribing information includes a boxed warning, stating that patients should be closely observed for an appropriate period of time after omalizumab administration.^[5] A joint task force of the AAAAI/ACAAI recommends direct observation for 2 hours after the first three omalizumab treatments and for 30 minutes after subsequent omalizumab treatments.^[46]

As mentioned in section 2, serum total IgE levels can remain elevated for up to 1 year after discontinuing omalizumab; therefore, pretreatment serum total IgE levels should be used to determine further dosage requirements after lapses in treatment of < 12 months. Local prescribing information should be consulted for additional information on dosage adjustments, use in special patient populations, precautions and contraindications.

8. Place of Omalizumab in the Management of Allergic Asthma

Current treatment guidelines advocate a stepwise approach in the management of patients with asthma, with the aim of achieving and maintaining control of symptoms by stepping up treatment as necessary, then stepping down therapy when the condition is well controlled for a reasonable period of time (e.g. ≥ 3 months).^[1–3,56] GINA global strategy for asthma management and prevention

(updated 2007) suggests that anti-IgE treatment with omalizumab could be considered for patients with persistent allergic asthma that remains inadequately controlled despite step 4 treatment, which (in addition to inhaled rapid-acting β_2 -agonist as needed) includes a medium- or high-dose ICS plus a long-acting β_2 -agonist and additional controller medication if required.^[1] According to these guidelines, there is strong evidence that the addition of omalizumab to other controller medications improves control of allergic asthma in patients whose disease is inadequately controlled with combinations that include high-dose ICSs or oral glucocorticoids.^[1]

Well designed clinical trials in patients with moderate to severe allergic asthma, along with the INNOVATE trial in patients with severe disease, have shown that add-on therapy with omalizumab reduced the incidence of asthma exacerbations and the need for ICSs, and improved asthma symptoms, lung function and asthma-related QOL compared with placebo (section 4). In addition, patient and physician global assessment of the effectiveness of therapy consistently favored omalizumab over placebo. Omalizumab also reduced asthma exacerbations and improved both AQLQ and RQLQ scores in patients with concomitant moderate to severe allergic asthma and persistent allergic rhinitis in the SOLAR study (section 4.3).^[21] In general, omalizumab was well tolerated in clinical trials, with most adverse events being of mild or moderate severity (section 5).

Along with these positive findings from clinical trials with omalizumab, there are also some practical concerns related to the use of omalizumab therapy in clinical practice. One issue is the high acquisition cost of the drug, which has led to a number of pharmacoeconomic analyses being conducted with omalizumab (section 6). Results of cost-effectiveness analyses with omalizumab have been highly variable, with some analyses suggesting that omalizumab is a cost-effective treatment strategy (i.e. below or at least close to commonly used thresholds of cost effectiveness) when used as indicated, but others suggesting unfavorable results. Some of these discrepancies might be attributed to differences between analyses in study perspective, geographical location, year of costing and, perhaps most importantly, sources of data used to derive clinical outcomes and healthcare resource use. Further study appears to be warranted in this area to better define the cost effectiveness of omalizumab.

Other practical considerations related to omalizumab treatment include the rare possibility of anaphylaxis, necessitating close monitoring of patients after administration (section 5), the need for subcutaneous administration, and the exclusion of patients with pretreatment serum total IgE levels <30 or >700 IU/mL for treatment with omalizumab (section 7). Although omalizumab is not approved for patients with baseline IgE levels <30 or >700 IU/mL,

the SOLAR trial allowed for the inclusion of patients with IgE levels as high as 1300 IU/mL. Data on the use of omalizumab in patients with low IgE levels appear to be limited to a modeled analysis that suggests higher doses of anti-IgE may be required if such therapy were to be used in these patients.^[57]

Another concern expressed by some experts is that, although add-on therapy with omalizumab has demonstrated statistically significant benefits in terms of reducing asthma exacerbations and ICS use in clinical trials, the absolute differences between omalizumab and placebo or BSC have been relatively modest from a clinical perspective.^[32,58] This may be related, in part, to a marked placebo effect observed in the trials, possibly resulting from better adherence with ICS therapy because of frequent (protocol-driven) physician visits.^[58] Nevertheless, omalizumab was consistently associated with favorable results in terms of patient and physician assessment of effectiveness, as well as clinically significant effects on asthma-related QOL (section 4). Arguably, these secondary outcomes may provide a useful overall assessment of the clinical efficacy of omalizumab in patients with moderate to severe allergic asthma.

In addition to international treatment guidelines mentioned earlier in this section, other sources have provided suggestions regarding the place of omalizumab in the management of patients with allergic asthma,^[59-63] although most of these recommendations reflect the results of clinical trials and approved indications specified in EU or US labeling. In some cases, however, analyses were conducted in an effort to predict which patients might benefit most from omalizumab treatment.^[40,64,65] Results of two pooled analyses by Bousquet and colleagues^[40,64] showed that patient baseline features that portend a response to omalizumab are those characterizing more severe disease, including a recent history of emergency asthma treatment, the use of high doses of ICS, and a low FEV₁. In a more recent analysis by this group, the only consistent predictor of response in the INNOVATE study was baseline total IgE levels (i.e. lower baseline IgE was associated with a smaller treatment benefit), although this finding was only partially supported in an analysis of data from a large pooled population.^[65] Responders to omalizumab could, however, be identified by physician's overall assessment of treatment, suggesting that this may be a useful way to determine whether omalizumab treatment should be continued beyond the initial 16-week period.^[65] This latter finding could be of practical importance since a 16-week assessment of response to omalizumab is mandated in the EU before further treatment with omalizumab is allowed (section 7).

Interestingly, little or no information was provided regarding comorbidities, such as respiratory infections or gastroesophageal reflux, in the clinical trials with omalizumab. Respiratory infec-

tions, for example, can provoke wheezing and increased asthma symptoms in many patients, and asthma symptoms can persist for weeks after the infection is cleared.^[1] Subgroup analyses would be of interest to evaluate the efficacy of omalizumab in patients with moderate to severe allergic asthma who have complications such as these. Another area of future research is the potential disease-modifying effects of omalizumab, as suggested by results of a small study in patients with allergic asthma who had received long-term treatment with omalizumab for ≈6 years and had discontinued therapy for ≈12–14 months.^[66] Despite not having received omalizumab for a year or more, most of the patients had only mild asthma, and some patients had downregulation of basophil (and probably mast cell) reactivity. Further study appears to be warranted in this area.

There are also a number of areas regarding the use of omalizumab that are beyond the scope of this review. Omalizumab is currently not approved for use in asthmatic children <12 years of age or for the management of other atopic diseases, although, as reviewed elsewhere, encouraging results have been reported for the efficacy and safety of omalizumab in pediatric allergic asthma and in the treatment of patients with allergic rhinitis.^[22,67] Also, for patients with concomitant allergic asthma and allergic rhinitis in the SOLAR trial,^[21] omalizumab provided beneficial effects for both conditions (section 4.3).

In conclusion, results of several large randomized trials have established omalizumab as an effective and well tolerated agent for use as add-on therapy in patients with severe persistent allergic asthma (EU labeling) or those with moderate to severe disease (US labeling). In addition, international treatment guidelines acknowledge the importance of omalizumab as a treatment option in these difficult-to-treat patient populations.

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