

Omalizumab: A Review of its Use in Patients with Severe Persistent Allergic Asthma

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Abstract Omalizumab (Xolair®) is a subcutaneously administered monoclonal antibody that targets circulating free IgE and prevents its interaction with the high-affinity IgE receptor (FcεRI), thereby interrupting the allergic cascade. In the EU, the drug is approved as add-on therapy in adults, adolescents and children aged ≥ 6 years with severe persistent allergic asthma. In well designed clinical trials, add-on omalizumab significantly reduced the asthma exacerbation rate (primary endpoint) compared with placebo in adults, adolescents and children with severe persistent allergic asthma. Furthermore, add-on omalizumab reduced the need for inhaled corticosteroids in adults and adolescents, and improved asthma control and symptoms, and asthma-related quality of life in all age groups. The efficacy of omalizumab was also demonstrated in the real-world setting, with add-on therapy leading to reduced rates of hospitalizations, emergency room visits and unscheduled doctor's visits, as well as improvements in asthma symptom scores and the physician's overall assessment of treatment response. More data are needed to determine the optimum duration of treatment, and currently the duration is at the discretion of the treating physician. Omalizumab was generally well tolerated in clinical trials; the most common adverse event was transient injection-site reactions. In cost–utility analyses modelled over a life-time horizon, add-on omalizumab was cost

effective compared with standard therapy, with incremental cost-effectiveness ratios falling within generally accepted willingness-to-pay thresholds. Thus, in difficult-to-treat patients with severe persistent allergic asthma, omalizumab provides a valuable treatment option.

Add-on omalizumab in severe persistent allergic asthma: a summary

Effectively reduces exacerbations and asthma symptoms in adults, adolescents and children (aged ≥ 6 years)
Reduces need for inhaled corticosteroids
Improves asthma-related quality of life
Reduces rate of hospitalizations and emergency room visits
Generally well tolerated
Considered cost effective compared with standard therapy alone

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1 Introduction

Asthma is a chronic inflammatory disorder of the airways that is estimated to affect 300 million people worldwide [1]. Severe asthma is estimated to occur in about 10 % of this population, and a substantial proportion of severe cases are attributable to allergic IgE-mediated mechanisms [2]. The clinical spectrum of asthma is highly variable, but airway inflammation, involving several inflammatory cells and multiple mediators, is a consistent feature. Airway hyper-responsiveness and structural changes are also components of the disease [1].

Asthma severity is classified on the basis of the intensity of treatment required to achieve good control of symptoms

[1]. Mild and moderate persistent asthma can generally be controlled with low-dose inhaled corticosteroids (ICS) and a long-acting β_2 -adrenergic agonist (LABA), whereas severe persistent asthma is often not well controlled with these treatments. Asthma is generally classified as severe when Global Initiative for Asthma (GINA) step 4 treatment (i.e. as-needed reliever medication plus medium- or high-dose ICS plus LABA [with or without other controller medications such as theophylline or a leukotriene receptor antagonist]) is required to maintain good control, or where good control is not achieved despite this high-intensity treatment [1].

Omalizumab (Xolair[®]) is a subcutaneously administered, humanized IgE monoclonal antibody that targets the allergic asthma inflammatory processes that underlie the symptoms observed in patients with severe persistent allergic asthma. In the EU, it is approved as add-on therapy (i.e. together with an ICS and LABA) for adults, adolescents and children aged ≥ 6 years with severe persistent, inadequately controlled allergic asthma [3]. This article focuses on the clinical use of omalizumab in these patient populations, with a brief summary of its pharmacological properties. A discussion of omalizumab in patients with moderate to severe allergic asthma (i.e. the approved indication in the USA and some other countries) is outside the scope of this review, although some data in this population are included in the tolerability section (Sect. 5).

Data sources: Medical literature (including published and unpublished data) on omalizumab in patients with severe allergic asthma was identified by searching databases (including MEDLINE and EMBASE) for articles published from 1996 to 14 June 2013, bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). No language restrictions were applied. Additional information (including contributory unpublished data) was also requested from the company developing the drug.

Search terms: ‘Omalizumab’ and ‘severe allergic asthma’

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

Keywords: Omalizumab, cost utility, pharmacodynamics, pharmacokinetics, severe allergic asthma, therapeutic use, tolerability.

2 Pharmacodynamic Properties

The pharmacodynamic properties of omalizumab in allergic asthma have been reviewed in detail elsewhere [4–6]; therefore, this section contains a brief overview, with a focus on recent data.

2.1 Mechanism of Action

Omalizumab is a recombinant DNA-derived humanized monoclonal antibody [5]. The drug selectively binds to the C ϵ 3 domain of free IgE, markedly decreasing levels of free IgE and preventing its interaction with the high-affinity IgE receptor (FC ϵ RI), primarily on mast cells and basophils, thereby interrupting the allergic cascade [5]. The reduction in levels of free IgE following omalizumab administration leads to a reduction in the expression of FC ϵ RI on inflammatory cells and, ultimately, a reduction in sputum and tissue eosinophilia [6, 7]. Omalizumab does not bind to and cross-link cell-bound IgE, which would cause degranulation of mast cells and basophils and, therefore, amplify the allergic cascade [6].

2.2 Effects on IgE and Inflammatory Markers in Asthma

In vitro, omalizumab inhibited IgE-induced upregulation of FC ϵ RI levels and FC ϵ RI-mediated histamine release on human skin mast cells [8]. In patients with severe allergic asthma, omalizumab treatment added to ICS for 16 weeks significantly reduced FC ϵ RI expression on basophils ($p < 0.01$) and plasmacytoid dendritic cells ($p = 0.029$) compared with placebo [9]. However, the reduction in FC ϵ RI expression did not correlate with an improved clinical response, as determined by asthma symptoms [9]. Treatment of allergic individuals with omalizumab for 12 weeks suppressed FC ϵ RI-mediated production by basophils of Th2 cytokines (interleukin [IL]-4, IL-13) and selected chemokines (IL-8, RANTES [regulated on activation, normal T-cell expressed and secreted]), which returned to pre-treatment levels after omalizumab was withdrawn [10].

In patients ($n = 45$) with mild to moderate asthma who underwent bronchoscopic evaluations before and after 16 weeks of treatment, compared with placebo, omalizumab was associated with significant ($p \leq 0.05$) reductions in serum free IgE levels; the number of IgE cells in airway mucosa; tissue eosinophil numbers; CD3⁺, CD4⁺ and CD8⁺ T lymphocytes; B lymphocytes and cells staining for IL-4 [7]. However, omalizumab was not associated with an improvement in airway hyper-responsiveness following a methacholine challenge [7, 11]. In a

pooled analysis of data from five randomized, double-blind trials in patients with moderate to severe allergic asthma receiving moderate to high doses of ICS, eosinophil counts were significantly ($p < 0.0001$) reduced from baseline with omalizumab but not with placebo [12]. Reduced peripheral blood eosinophil counts were associated with improved clinical outcomes, including a reduction in the mean number of asthma exacerbations requiring treatment with corticosteroids [12].

RANTES and eotaxin concentrations in exhaled breath condensate, fractional exhaled nitric oxide (FeNO), serum eosinophil cationic protein and blood eosinophil counts were also significantly decreased after 16 weeks of omalizumab compared with pre-treatment levels ($p < 0.05$ to <0.001) in patients with severe allergic asthma [13, 14]. Levels of peripheral T lymphocytes positive for granulocyte macrophage colony-stimulating factor (GM-CSF), and IL-2 and IL-13 lymphocytes were reduced to a significantly greater extent after 12 weeks of omalizumab treatment than after placebo ($p < 0.05$ for all) [15].

Exploratory retrospective analyses of data from the EXTRA study [16] (Sect. 4.1.1) indicate that levels of the Th2 inflammatory biomarkers FeNO, peripheral blood eosinophil counts and serum periostin may be useful in identifying patients with severe allergic asthma most likely to respond to omalizumab treatment [17]. Treatment effect on protocol-defined asthma exacerbations was compared after 48 weeks of treatment in patients divided into subgroups of low- and high-biomarker levels at baseline. The difference in exacerbation rate between omalizumab and placebo groups was significant in the three high-biomarker level subgroups ($p < 0.07$ to <0.001), but not in the low-biomarker level subgroups, suggestive of a greater treatment benefit with omalizumab in patients with higher levels of these biomarkers [17].

Recent evidence from a modelled analysis indicates that IgE production decreases over time during omalizumab treatment (54 % per year) suggesting that indefinite treatment may not be required (see Sect. 8) [18]. While omalizumab significantly reduced free serum IgE levels from baseline after 16 weeks of treatment ($p < 0.001$), there was no correlation between free serum IgE levels and treatment response [19].

Chronic airway inflammation is thought to result in airway remodelling in patients with severe asthma and, while there are limited data on the effects of omalizumab on this complex process [20], evidence suggests that it may have the potential to reduce airway remodelling. In a 16-week study using computed tomography to determine airway thickness in patients with severe asthma ($n = 30$), omalizumab plus conventional asthma therapy was associated with reduced airway wall thickness ($p < 0.01$) compared with conventional therapy alone [21].

Furthermore, decreased wall thickness was associated with more favourable clinical outcomes, such as improvements in forced expiratory volume in 1 s (FEV₁). In patients ($n = 11$) with severe persistent allergic asthma, there was a significant ($p < 0.05$) decrease in mean reticular basement membrane thickness after 12 months' omalizumab treatment compared with pre-omalizumab treatment, as determined in bronchial biopsies [22].

In clinical studies, serum free IgE levels were reduced in a dose-dependent manner within 1 hour of omalizumab administration, and reduced levels were maintained between doses [3]. IgE levels returned to pre-treatment levels 1 year after omalizumab was discontinued, and there was no evidence of a rebound in IgE levels after a washout of the drug [3].

3 Pharmacokinetic Properties

The following summary of pharmacokinetic properties is taken from studies in adult and adolescent patients with allergic asthma that are reported in the European Medicines Agency's Summary of Product Characteristics (SPC) [3].

The mean absolute bioavailability of omalizumab after subcutaneous administration is 62 % [3]. The drug is absorbed slowly, and following a single subcutaneous dose, peak serum concentrations were reached after a mean of 7–8 days [3]. Linear pharmacokinetics were observed at omalizumab doses >0.5 mg/kg. At steady state, area under the serum concentration-time curve (AUC) values from day 0 to 14 were up to 6-fold higher than those calculated after the first dose. Similar serum concentration-time profiles of omalizumab were observed when the drug was administered as a lyophilised or liquid formulation [3]. Following subcutaneous administration, the apparent volume of distribution in patients with asthma was 78 ± 32 mL/kg [3].

Omalizumab had a mean serum elimination half-life of 26 days in patients with asthma [3]. The mean apparent clearance was 2.4 ± 1.1 mL/kg/day, although clearance was approximately doubled when body weight doubled. Omalizumab clearance involves IgG clearance processes and is also dependent on clearance via specific binding and complex formation with IgE, which is eliminated via the liver and in bile.

Population pharmacokinetic data show that dosage adjustment of omalizumab is not required based on age (6–76 years), ethnicity or sex [3]. No pharmacokinetic data are available on the use of omalizumab in patients with hepatic or renal impairment [3]. The use of omalizumab in pregnant women has not been adequately studied, and the drug should not be used in this population unless clearly necessary [3].

There is little potential for interactions between omalizumab and other agents as cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the drug's clearance [3]. In clinical studies, the safety of omalizumab was not altered when co-administered with commonly prescribed asthma medications.

4 Therapeutic Efficacy

The therapeutic efficacy of subcutaneous omalizumab as add-on therapy with ICS-based treatment has been evaluated in several clinical trials in adults and adolescents (aged ≥ 12 years) (Sect. 4.1), and children (aged ≥ 6 years) (Sect. 4.2) with severe persistent allergic asthma.

The omalizumab dose was based on body weight and pre-treatment total serum IgE levels, as recommended in the prescribing information [3]. The dose is calculated to ensure that patients receive at least 0.016 mg/kg/IgE (IU/mL) every 4 weeks, and injections were administered monthly, or every 2 weeks for higher dosages.

4.1 Adults and Adolescents

4.1.1 Randomized Studies

Eligible patients were aged 12–75 years (mean age 39–46 years) with severe persistent allergic asthma with objective evidence of an allergy to ≥ 1 perennial aeroallergen and inadequately controlled with ICS [16, 23–26]. Patients were required to have a total serum IgE level of ≥ 30 to ≤ 700 IU/mL [16, 23–26] (subsequent to these trials, the baseline range of total serum IgE levels determining eligibility for omalizumab treatment was increased [Sect. 7]). Where stated, patients were also required to have a baseline FEV₁ of ≥ 40 and < 80 % of the predicted normal value [16, 23–25] and ≥ 12 % reversibility in FEV₁ within 30 min of administration of a short-acting β_2 -adrenergic agonist (SABA; otherwise referred to as rescue medication) [23–25]. Exclusion criteria included elevated IgE levels for reasons other than atopy [16, 23–26], < 3 months of therapy with stable doses of immunosuppressants [23, 25] and a smoking history of ≥ 10 pack years [16, 24, 25]. In all studies, patients continued treatment with ICS and rescue medication with SABAs was permitted. Patients were able to continue LABA therapy in all studies except one [23], and continued stable doses of theophylline or anti-leukotrienes were allowed in all studies except two [23, 26].

The primary efficacy endpoints included the exacerbation rate (generally defined as a worsening of asthma symptoms and a requirement for treatment with systemic corticosteroids or double the baseline ICS dose; see Table 1) [16, 23, 24], the corticosteroid sparing effect [26]

and persistence of response (as determined by the physician's global evaluation of treatment effectiveness [GETE]; defined in Table 2) [25]. Analyses were performed in the intent-to-treat (ITT) populations, although the INNOVATE study evaluated patients randomized subsequent to a protocol amendment (primary ITT population) based on changes to GINA guidelines [24]. Also in the INNOVATE study, a difference between treatment groups in asthma exacerbation rates in the year prior to the study was noted, so a post hoc adjustment was made to the primary endpoint analysis to factor in these differences [24].

4.1.1.1 Exacerbations The per patient asthma exacerbation rate was significantly lower in patients treated with add-on omalizumab than with placebo in all studies evaluating this outcome as the primary endpoint, with relative reductions ranging from 25 to 48 % (Table 1) [16, 23, 24].

In the study by Busse et al. [23], the efficacy of omalizumab versus placebo was evaluated during an initial 16-week period when beclomethasone dipropionate (BDP) doses were kept stable followed by a 12-week corticosteroid-reduction phase during which BDP doses were reduced by approximately 25 % of the baseline dose every 2 weeks for 8 weeks until treatment was discontinued or asthma symptoms worsened [23]. On study entry, each patient had been switched from their current ICS dose to the equivalent dose of BDP. During the corticosteroid-stable and -reduction phases, the asthma exacerbation rate was significantly lower in the omalizumab group than in the placebo group (Table 1). Furthermore, during a double-blind, placebo-controlled, 24-week extension phase ($n = 460$), the significant difference in favour of omalizumab was maintained, and this was despite sustained significant ($p < 0.001$) reductions in the use of ICS achieved during the corticosteroid-reduction phase [27]. During the extension phase, the exacerbation rate in the omalizumab and placebo groups was 0.60 versus 0.83 ($p = 0.023$) per patient and the proportion of patients experiencing at least one exacerbation was 31.8 versus 42.8 % ($p = 0.015$) [27].

Also in the study by Busse et al. [23], significantly fewer omalizumab recipients than placebo recipients experienced at least one asthma exacerbation in the corticosteroid-stable (14.6 vs. 23.3 %; $p = 0.009$) and -reduction (21.3 vs. 32.3 %; $p = 0.004$) phases. Furthermore, the mean duration of exacerbations was shorter with omalizumab than with placebo in the corticosteroid-stable (7.8 vs. 12.7 days; $p < 0.001$) and -reduction (9.4 vs. 12.6 days; $p = 0.021$) phases [23].

The 25 % relative reduction in the asthma exacerbation rate achieved with omalizumab versus placebo in the 48-week study by Hanania et al. [16] (EXTRA study; Table 1) was accompanied by a significantly increased

Table 1 Efficacy of add-on omalizumab on the asthma exacerbation rate in patients with severe persistent allergic asthma

Reference [trial name]	Design	Duration (weeks)	Treatment	Pt no.	Mean FEV ₁ (% of predicted) at BL	Exacerbations/pt ^a	RR in exacerbations/pt ^a vs. PL (%)
<i>Adults and Adolescents</i>							
Bousquet et al. [25]	r,ol,mc	32	OMA	272	63.0	0.55***	44
			OAT	128	61.1	0.98	
Busse et al. [23]	r,db,mc	16 [CSS phase]	OMA	268	68.2	0.28** ^{.b}	48
			PL	257	67.7	0.54	
		12 [CSR phase]	OMA	268		0.39** ^{.b}	41
			PL	257		0.66	
Hanania et al. [16] [EXTRA]	r,db,mc	48	OMA	427	65.4	0.66** ^{.b}	25
			PL	421	64.4	0.88	
Holgate et al. [26]	r,db,mc	16 [CSS phase]	OMA	126	62.9	0.15	35
			PL	120	66.0	0.23	
		16 [CSR phase]	OMA	126		0.19	44
			PL	120		0.34	
Humbert et al. [24] [INNOVATE]	r,db,mc	28	OMA	209	61.0	0.68* ^{.b}	26
			PL	210	61.6	0.91	
<i>Children (aged 6 to <12 years)</i>							
Kulus et al. [28]	Sub-analysis ^c	24 [CSS phase]	OMA	159	81.8	0.42* ^{.b}	34
			PL	76	82.6	0.63	
		28 [CSR phase]	OMA	159		0.29***	63
			PL	76		0.77	
		52 [total]	OMA	159		0.73***	50
			PL	76		1.44	

Results are shown for the ITT populations, except for the INNOVATE study, which shows results for the population randomized after a protocol amendment (primary ITT)

OMA or PL were administered in addition to standard asthma therapy

BL baseline, CS corticosteroids, CSR CS reduction, CSS CS stable, db double blind, FEV₁ forced expiratory volume in 1 s, ICS inhaled CS, ITT intent to treat, mc multicentre, OAT optimized asthma therapy, ol open label, OMA omalizumab, PL placebo, pt/s patient/s, r randomized, RR relative reduction

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. PL or OAT

^a Exacerbations were defined as a worsening of asthma symptoms, as determined by the requirement for treatment with systemic CS [16, 23–26, 28], and/or doubling of baseline ICS dose [23, 28], or an increase of ≥ 20 mg/day of oral CS [16]

^b Primary endpoint

^c Results are from a sub-group analysis of children with uncontrolled severe, allergic asthma who were part of a large randomized, double-blind study in children with moderate to severe allergic asthma [29]

time to the first asthma exacerbation in the group receiving omalizumab (hazard ratio 0.74; 95 % CI 0.60–0.93; $p = 0.008$).

As well as the 26 % relative reduction in the asthma exacerbation rate achieved with omalizumab versus placebo in the 28-week study by Humbert et al. [24] (INNOVATE study; Table 1), severe exacerbations (peak expiratory flow [PEF] or FEV₁ <60 % of personal best, requiring treatment with systemic corticosteroids) (0.24 vs. 0.48; $p = 0.002$) and emergency room visits for asthma (0.24 vs. 0.43; $p = 0.038$) were also significantly reduced with omalizumab versus placebo.

Two 32-week studies evaluated asthma exacerbations as secondary endpoints [25, 26]. In the study by Bousquet et al. [25], there were significantly fewer exacerbations (Table 1), severe exacerbations ($p = 0.023$) and hospitalizations for asthma exacerbations ($p = 0.037$) in the omalizumab group than in the optimized asthma therapy (OAT) group (optimized according to GINA 2004 step 4 treatment guidelines). The study by Holgate et al. [26] reported a 35 and 44 % lower exacerbation rate with omalizumab than with placebo in the corticosteroid-stable and –reduction phases, respectively, but the difference did not reach statistical significance.

Table 2 Description of asthma rating scales used in randomized and observational studies

Rating scale	Description
Asthma control questionnaire (ACQ) [25, 31, 35]	7-item questionnaire assessing 5 asthma symptoms, rescue medication use and FEV ₁ ; scores range from 0 (totally controlled) to 6 (severely uncontrolled); a minimum important improvement is a decrease of ≥ 5 points [36]
Asthma control test (ACT) [31–33]	5-item survey assessing asthma interference with activities, shortness of breath, nocturnal symptoms, rescue medication use and self-rating of asthma control; scores range from 5 (poorly controlled) to 25 (well controlled); a minimum important improvement is an increase of ≥ 3 points [34]
Asthma quality-of-life questionnaire (AQLQ) [16, 24, 26, 31, 32, 37–39]	32-item questionnaire assessing 4 domains (symptoms, activity limitation, emotional function and environmental stimuli); scores range from 1 (severely impaired) to 7 (no impairment); a minimum clinically important improvement is an increase of ≥ 0.5 points [36]
Asthma symptom score [26]	Total of daytime and nocturnal scores and morning asthma symptom score; scores range from 0 (well controlled) to 9 (poorly controlled); a decrease, therefore, reflects improvement
Mini-AQLQ [31, 33]	15-item questionnaire derived from and assessing same domains as the AQLQ; scores range from 1 (severely impaired) to 7 (no impairment); a minimum clinically important improvement is ≥ 0.5 points [40]
Physician's global evaluation of treatment effectiveness (GETE) [25, 28, 31, 35, 39, 41]	Overall clinical evaluation of asthma control based on all available information, including patient interview, physical examination, spirometry, review of medical notes and patient's diary (if used); patients with a rating of excellent or good are classified as responders, while those with a rating of moderate or poor, or with worsening asthma are classified as nonresponders

FEV₁ forced expiratory volume in 1 s

Exacerbation results from randomized trials are supported by a pooled analysis [30] of data from seven clinical trials that included 4,308 patients, of whom 93 % were classified as having severe persistent asthma according to GINA 2002 classification. Compared with control (standard asthma therapy plus placebo or standard therapy alone), omalizumab significantly reduced the asthma exacerbation rate (38 %) and rate of emergency room visits (47 %) ($p < 0.0001$ for both) [30]. Subgroup analyses demonstrated that the efficacy of omalizumab with regard to asthma exacerbations was unaffected by age, gender, baseline serum IgE levels above or below the median, or by a 2- or 4-weekly dosing schedule.

4.1.1.2 Corticosteroid Sparing Effect The inhaled fluticasone dose was reduced significantly more from baseline (primary endpoint) in patients receiving add-on omalizumab than in those receiving placebo, without worsening of symptoms or an increase in rescue medication use, in the 32-week study by Holgate et al. [26], which comprised a 16-week corticosteroid-stable phase followed by a 16-week corticosteroid-reduction phase. All patients had switched to fluticasone during the run-in period and all had required $\geq 1,000$ $\mu\text{g/day}$ for symptom control. In the first 12 weeks of the corticosteroid-reduction phase, fluticasone was reduced by 250 $\mu\text{g/day}$ at 2-week intervals if tolerated, and the final 4 weeks were used to assess if the reduced dosage could be maintained. The mean reduction in the dose of fluticasone was 57.2 % in the omalizumab group compared

with 43.3 % in the placebo group ($p = 0.003$), and the proportion of patients who were able to reduce their fluticasone dose by ≥ 50 % was 73.8 versus 50.8 %, respectively ($p = 0.001$). By study end, 60.3 % of patients in the omalizumab group and 45.8 % of patients in the placebo group were taking fluticasone at a dosage of ≤ 500 $\mu\text{g/day}$ ($p < 0.05$) [26].

Similar results were reported in the 28-week study by Busse et al. [23]. The median reduction in BDP dose in the omalizumab and placebo groups was 75 versus 50 % ($p < 0.001$), and a ≥ 50 % reduction in BDP dose was achieved in 72.4 versus 54.9 % of patients ($p < 0.001$) [23]. BDP was discontinued in 39.6 versus 19.1 % of patients, respectively ($p < 0.001$). During the 24-week extension [27] of this study [23], patients in the omalizumab group maintained significantly lower use of ICS than patients in the placebo group, with a mean BDP equivalent dose of 227 versus 335 $\mu\text{g/day}$ ($p < 0.001$) [27].

4.1.1.3 Asthma Symptom Control and Rescue Medication Use Overall, randomized studies demonstrated a significantly greater improvement in asthma control and rescue medication use in patients treated with add-on omalizumab than with placebo [16, 23–26]. For example, in the study by Holgate et al. [26], the asthma symptom score (defined in Table 2) improved more in the omalizumab than placebo group throughout the corticosteroid-stable (first 16 weeks) and -reduction (final 16 weeks) phases, with significant treatment differences at most time points, including weeks

4, 8, 12, 18, 26, 30 and 32 ($p < 0.05$ for all) [26]. Similarly the use of rescue medication was reduced from baseline significantly more with omalizumab than placebo, and differences were significant from week 8 to study end ($p \leq 0.05$ to <0.001) [26]. The change from baseline in mean morning PEF was not significant in either treatment group at any time point, but the difference between groups significantly favoured omalizumab versus placebo at weeks 20 and 30 ($p < 0.05$). FEV₁ measurements throughout the study showed significant differences in favour of omalizumab versus placebo at weeks 4, 20, 28 and 30 (p values not stated) [26].

The overall score on the Asthma Control Questionnaire (ACQ; defined in Table 2) improved from baseline significantly more in the omalizumab group than the OAT group at week 16 and study end ($p < 0.001$ for both) in the 32-week, persistency-of-response study by Bousquet et al. [25] (see Sect. 4.1.1.5). Among those that responded at week 16, the least squares mean (LSM) change from baseline in the ACQ overall score at week 16 and 32 was -1.03 and -1.13 in the omalizumab group, and -0.42 and -0.45 in the OAT group ($p < 0.001$ for both) [25]. Furthermore, patients in the omalizumab group experienced fewer night-time awakenings in the 2 weeks prior to the 32-week assessment than patients in the OAT group ($p = 0.039$). Also in this study, the mean FEV₁ (% predicted) was significantly greater in the omalizumab group than in the OAT group at week 16 (68.4 vs. 64.8 %; $p = 0.024$) and week 32 (68.1 vs. 63.7 %; $p = 0.007$) [25].

Similarly, significantly greater improvements from baseline in FEV₁ (% predicted) were demonstrated in the omalizumab group than the placebo group ($p < 0.001$ to <0.019) throughout the 28-week study by Busse et al. [23], and differences continued to significantly favour omalizumab at weeks 32, 36, 40 and 44 ($p < 0.05$ to <0.005) of the 24-week extension study [27].

4.1.1.4 Effect on Asthma-Related Quality of life In randomized studies that evaluated asthma-related quality of life (QOL), patients receiving add-on omalizumab had greater improvements in this endpoint than patients receiving placebo [16, 24, 26, 37]. QOL was assessed using the Asthma QOL Questionnaire (AQLQ; defined in Table 2) [42].

Throughout 52 weeks of treatment (including the 28-week core study by Busse et al. [23] and a 24-week extension [27]), all 4 domains of the AQLQ, as well as the overall AQLQ score, improved significantly ($p < 0.05$ to <0.001) more in the omalizumab group than in the placebo group during the corticosteroid-stable, -reduction and extension phases [37]. Furthermore, a greater ($p < 0.05$ to <0.001) proportion of patients in the omalizumab group than the placebo group achieved a

clinically meaningful (≥ 0.5) or large (≥ 1.5) improvement in the overall score and most individual domain scores during each phase.

Similar results were reported in two other studies, with a clinically meaningful improvement in the AQLQ overall score in 58 % of patients in the omalizumab group versus 39 % of patients in the placebo group ($p < 0.01$) after 32 weeks' treatment in the study by Holgate et al. [26], and 61 versus 48 % of patients ($p = 0.008$), respectively, after 28 weeks' treatment in the INNOVATE study [24]. In the omalizumab and placebo groups in the corresponding studies, large improvements were reported in 16 versus 6 % of patients ($p < 0.05$) [26] and 28 versus 17 % of patients ($p = 0.011$) [24]. A post hoc analysis of data from the INNOVATE study revealed that the mean total symptom score strongly correlated with the AQLQ overall score ($r = 0.503$) [43].

After 48 weeks of treatment in the EXTRA study [16], the difference between omalizumab and placebo groups (using a mixed-effects model) in the AQLQ score was 0.29 points (95 % CI 0.15, 0.43) in favour of omalizumab [16]. Furthermore, at week 48, more patients receiving omalizumab than placebo had an improvement from baseline in their AQLQ score that exceeded the minimum clinically important difference (≥ 0.5) (67.8 versus 61.0 %; $p = 0.042$) [16].

These results are supported by a pooled analysis [38] of six controlled clinical trials that included 2,548 patients, of whom 96 % were classified as having severe persistent asthma according to GINA 2002 classification. Add-on omalizumab was associated with significantly greater improvements in the AQLQ total score than current asthma therapy alone (1.01 vs. 0.61 points; $p < 0.001$) and more patients receiving omalizumab than their current asthma therapy alone achieved a clinically meaningful improvement (66.3 vs. 52.4 %; $p < 0.001$) [38].

4.1.1.5 Persistence of Response Response to add-on omalizumab after 16 weeks of therapy, as assessed by a rating of good or excellent on the physician-rated GETE, effectively predicted continued response to omalizumab (primary endpoint) in most patients in the study by Bousquet et al. [25]. According to the GETE in the modified ITT population (all randomized patients with at least one post baseline efficacy assessment), 190 of 261 patients (72.8 %) in the omalizumab group and 29 of 93 patients (31.2 %) in the OAT group were classified as responders at week 16 ($p < 0.001$). At week 32, 199 of 259 patients (76.8 %) and 25 of 104 patients (24.0 %) were classified as responders in each group, respectively ($p < 0.001$). Significantly more patients in the omalizumab group (62.9 %) than in the OAT group (14.1 %) were classified as responders at both weeks 16 and 32 ($p < 0.001$) [25].

Among responders at week 16 in the omalizumab group, 91.4 % had a persistent response at week 32 [25]. In contrast, the persistency of response at week 32 in the OAT group was 64.3 %. Data demonstrated that a patient who responded to omalizumab at week 16 was 10.7 times (95 % CI 8.01–14.27) more likely to continue to respond at week 32 than to stop responding, and 17.4 times (95 % CI 8.64–35.13) more likely to respond at week 32 than those who did not respond at week 16 [25].

A pooled analysis of data from seven randomized controlled trials (93 % of patients were classified as having severe persistent allergic asthma) found that the most meaningful predictor of response to omalizumab therapy is the physician's GETE after 16 weeks of therapy [41].

4.1.2 Real-World Studies

Several multicentre, observational studies support results of randomized trials, demonstrating that omalizumab is effective as add-on therapy in patients with severe persistent allergic asthma in the real-world setting [31, 32, 35, 39, 44–47].

4.1.2.1 The eXpeRience Registry The 2-year, multinational, non-interventional eXpeRience registry evaluated data from 916 patients (ITT population) who were enrolled within 15 weeks of commencing add-on omalizumab treatment [31]. The mean age was 45 years and 65 % of patients were female. At baseline, maintenance therapy included oral corticosteroids (28 %), ICS (27 %), LABA (16 %), ICS/LABA (82 %), SABA (5 %), long-acting antimuscarinics (20 %) and leukotriene inhibitors (61 %) [31].

After treatment with omalizumab for 16 weeks, which was the prespecified time for the physician-rated GETE (defined in Table 2) ($n = 584$), 69.9 % of patients had an excellent or good response (classified as responders), and 30.1 % had a moderate or poor response or worsening asthma (classified as non-responders) [31]. Sixteen patients (1.7 %) stopped treatment at week 16 due to non-response. In the physician's GETE evaluated at any time during the study ($n = 915$), 64.2 % of patients were classified as responders and 30.7 % were classified as non-responders; 5.1 % did not have a GETE assessment.

The proportion of patients who did not experience a clinically significant or severe clinically significant exacerbation (defined in Table 3) in the previous year increased with omalizumab treatment and was markedly higher at months 12 and 24 than during the 12 months pre-treatment (Table 3) [31]. A similar pattern was observed in the subgroup of patients classified as responders, with the proportion of patients with no clinically significant asthma exacerbations in the previous year increasing from 4.9 pre-treatment to 82.4 % at month 12 and 81.9 % at month 24,

and the proportion with no severe clinically significant exacerbations in the previous year increasing from 27.4 to 95.8 and 95.6 %, respectively. Accordingly, among the total evaluable population, hospitalizations, emergency room visits and unscheduled doctor's visits were markedly lower at months 12 and 24 than during the pre-treatment period (Table 3).

The eXpeRience registry also demonstrated that add-on therapy with omalizumab was associated with a reduction in the use of oral CS maintenance therapy and rescue therapy, and marked improvements in asthma control and asthma-related QOL (Table 3).

4.1.2.2 Other Observational Studies In a recently published French analysis (Pharmacoepidemiology of Asthma and Xolair [PAX]), add-on omalizumab therapy was associated with significantly reduced rates of hospitalizations and emergency room visits compared with standard asthma therapy alone [47]. A total of 767 adults and adolescents (374 received omalizumab at least once and 393 were not prescribed omalizumab) with severe uncontrolled allergic asthma were followed up for a mean period of 20.4 months. The adjusted relative risk of hospitalizations or emergency room visits with omalizumab versus no omalizumab treatment was 0.57 (95 % CI 0.43–0.78) [47].

Similarly, following 12 months' treatment with omalizumab in an Italian analysis ($n = 142$), the annual rate of asthma exacerbations, emergency room visits and hospitalizations decreased by 79, 88 and 95 %, respectively, compared with the 12 months prior to omalizumab therapy [45]. Furthermore, 77 % of patients were rated as having a good or excellent treatment response on the GETE.

In the PERSIST study in Belgium, after 16 and 52 weeks of omalizumab treatment ($n = 158$), 91 and 66 % of patients, respectively, were severe-exacerbation free, 82 and 84 % had improvements in the total AQLQ score of ≥ 0.5 points, and 82 and 72 % had a good or excellent response on the physician-rated GETE ($p < 0.001$ vs. baseline for all comparisons) [39].

Several real-life studies in Germany have demonstrated results consistent with those in other observational analyses. After 16 weeks of omalizumab treatment in the X-CLUSIVE study ($n = 195$), mean FEV₁ (increased from 2.05 to 2.31 L) and percent predicted FEV₁ (increased from 63.6 to 73.7 %) improved significantly from baseline ($p < 0.05$ for both) [35]. The exacerbation rate (-74.9 %; $p < 0.0001$), days of absenteeism (-92.1 %; $p < 0.001$) and ACQ score (-43.7 %; $p < 0.0001$) also improved significantly from baseline, and investigators rated the response to omalizumab, using the GETE, as excellent or good in 78.8 % of patients [35]. Concomitant asthma medications were able to be adjusted in 53 % of patients, with theophylline, leukotriene antagonists and oral

Table 3 Results from the eXpeRience registry of patients (adults, adolescents and children aged ≥ 6 years) with severe persistent allergic asthma who received add-on omalizumab in a real-world setting; eXpeRience was a 2-year, international, single-arm, observational registry [31]

Outcome	Pt no. (pre-treatment/ month 12/ month 24)	Pre-treatment ^a	Month 12	Month 24
No clinically significant exacerbations ^b (% of pts)	916/ 734/ 643	6.8	54.1	67.3
No severe clinically significant exacerbations ^c (% of pts)	916/ 734/ 643	30.2	80.5	89.9
Clinically significant exacerbation rate ^b (per year)	847/ 686/ 620	4.9	1.0	0.6
Severe clinically significant exacerbation rate ^c (per year)	842/ 691/ 625	2.2	0.2	0.1
Mean no. asthma-related health-care uses (per year) ^d	882/ 702/ 628	6.2	1.0	0.5
Requiring maintenance OCS (% of pts)	916/ 734/ 643	28.6 ^e	16.1	14.2
Mean total daily OCS dose (mg)	916/ 734/ 643	15.5 ^e	7.7	5.8
Experiencing day-time symptoms (% of pts)	916/ 734/ 643	90.5 ^e	57.5	54.1
Experiencing night-time symptoms (% of pts)	916/ 734/ 643	79.6 ^e	30.7	25.3
Rescue medication use (% of pts)	916/ 734/ 643	87.0 ^e	54.1	49.8
Experiencing limitations of activities (% of pts)	916/ 734/ 643	86.0 ^e	46.6	41.7
ACQ score ^f	916/ 734/ 643	2.74 ^e	1.73	1.80
ACT score ^f	916/ 734/ 643	13.0 ^e	19.1	19.7
AQLQ score ^f	916/ 734/ 643	4.27 ^e	5.58	5.49
Mini-AQLQ score ^f	916/ 734/ 643	3.81 ^e	5.04	5.2

ACQ asthma control questionnaire, ACT asthma control test, AQLQ asthma quality-of-life questionnaire, OCS oral corticosteroids, pt/s patient/s

^a Unless stated otherwise, the pre-treatment period was the 12 months prior to the start of omalizumab treatment

^b Defined as a worsening of asthma symptoms that required treatment with oral or intravenous corticosteroids

^c Defined as a clinically significant exacerbation with a reduction in peak expiratory flow to <60 % of the patient's predicted or personal best

^d Includes hospitalizations, emergency room visits and unscheduled doctor's visits

^e Measured at start of omalizumab treatment

^f See Table 2 for definition

corticosteroids reduced in the course of the study, whereas doses of ICS and LABAs generally remained unchanged.

In a second German study ($n = 280$), omalizumab was associated with a significant reduction in daily asthma symptoms and night-time awakenings after 4 months ($p < 0.001$ for both), with a further reduction in both endpoints at 6 months ($p < 0.001$ vs. baseline for both) [44]. Accordingly, throughout 6 months of treatment, asthma exacerbations, emergency room visits and asthma-related QOL all improved significantly from baseline ($p < 0.001$ for all).

Omalizumab therapy over the long term (mean duration of 3.4 years) was associated with sustained improvement in asthma symptoms, according to preliminary results (reported in an abstract) from a long-term follow-up of omalizumab-treated patients ($n = 106$) in clinical practice in Germany [48]. Mean FEV₁ and asthma-related QOL scores improved significantly throughout treatment ($p < 0.001$) compared with pre-treatment results.

Interestingly, an additional German study ($n = 471$) demonstrated that the efficacy of omalizumab did not appear to be affected by age [46]. The exacerbation rate was significantly reduced compared with the pretrial period in patients aged ≥ 50 years (-69 %) and in patients aged < 50 years (-75 %) ($p < 0.001$ for both) after 4 months' treatment.

The retrospective APEX (Asthma Patient Experience on Xolair) study in clinical practice in the UK ($n = 136$) primarily evaluated the corticosteroid-sparing effect of omalizumab by comparing corticosteroid use in the 12 months pre- and post-omalizumab use [32]. During the 12 months following the initiation of omalizumab, compared with the period pre-omalizumab, the total quantity of oral corticosteroids prescribed decreased by 34 % ($p < 0.001$); 49 % of patients stopped oral corticosteroids completely and 64 % stopped or reduced use by >20 %. Significant improvements from the period pre-omalizumab to the 12 months following omalizumab initiation were also observed for the mean number of asthma exacerbations (3.67 vs. 1.7 events/year; $p < 0.001$), mean percent predicted FEV₁ ($n = 32$; 69.9 vs. 78.6 %; $p < 0.001$), asthma control test (ACT; defined in Table 2) score ($n = 15$; 11 vs. 20 points; p -value not reported) and AQLQ score ($n = 21$; 2.8 vs. 5.7 points; p -value not reported) [32].

4.2 Children

This section focuses on a prespecified subgroup analysis [28] of children aged 6 to < 12 years with uncontrolled severe allergic asthma who were part of a large randomized, double-blind, placebo-controlled study of add-on

omalizumab in children with moderate to severe allergic asthma [29]. Children were classified as having severe disease if their asthma was uncontrolled despite receiving high-dose ICS (≥ 500 $\mu\text{g/day}$ of fluticasone or equivalent) and a LABA, with or without other controller medications [28]. The uncontrolled nature of asthma was confirmed during the run-in period, and the omalizumab or placebo treatment period consisted of a 24-week corticosteroid-stable phase followed by a 28-week corticosteroid-reduction phase, during which the ICS dose could be reduced by 25–50 % once every 8 weeks. The primary efficacy measure was the rate of clinically significant asthma exacerbations (i.e. worsening of asthma symptoms requiring the baseline ICS dose to be doubled [although this is no longer recommended in treatment guidelines] and/or ≥ 3 days' treatment with systemic corticosteroids) during the corticosteroid-stable phase [28].

At baseline, 57 % of children were receiving anti-leukotriene therapy and 3 % were receiving maintenance oral corticosteroids [28]. In the year prior to study entry, children had experienced a mean of 2.8 exacerbations.

During the corticosteroid-stable and -reduction phases, there were significantly fewer clinically significant asthma exacerbations in the omalizumab group than in the placebo group, with a 34 and 63 % relative reduction, respectively (Table 1). Accordingly, throughout the total 52-week treatment period, the rate of exacerbations was significantly lower in the omalizumab group than in the placebo group (Table 1). The reduction in the ICS dose from baseline to the end of the corticosteroid-reduction phase was not significantly different between the omalizumab (−2.5 %) and placebo (−2.0 %) groups [28].

Clinically significant exacerbations were significantly reduced with omalizumab versus placebo in children with baseline predicted $\text{FEV}_1 < 80$ % (0.84 vs. 1.64; $p = 0.007$) and in children with baseline predicted $\text{FEV}_1 \geq 80$ % (0.66 vs. 1.35; $p = 0.012$) [28]. More patients in the omalizumab group than the placebo group were assessed as having an excellent or good response using the physician's GETE (74.2 vs. 55.3 %; $p < 0.001$).

A small, uncontrolled study of children and adolescents (aged 5–16 years) with severe allergic asthma in the UK found that after 16 weeks' treatment with add-on omalizumab, the median daily prednisolone dose reduced from 20 mg at baseline to 5 mg ($n = 34$) [33]. Furthermore, the mini AQLQ score (defined in Table 2) increased from 3.5 at baseline to 5.9 ($n = 24$) and the childhood ACT score increased from 12 to 20 points ($n = 23$) ($p < 0.0001$ for all comparisons).

Observational data from a 1-year, real-world multicentre survey ($n = 101$) in children and adolescents (aged 6 to <18 years) with severe allergic asthma in France reported generally greater benefits with add-on omalizumab than

those reported in clinical trials of omalizumab [49]. Asthma control (primary endpoint; defined according to current GINA criteria) improved significantly from baseline to weeks 20 and 52 in patients categorized as having good control (0, 53 and 67 % of patients, respectively), partial control (18, 30 and 25 %) or poor control (82, 17 and 8 %) ($p < 0.0001$) [49]. Only 14 % of patients did not show any improvement during treatment. Mean exacerbation rates decreased from 4.4 per patient in the 12 months before omalizumab was commenced to 1.25 during treatment ($p < 0.0001$), equating to a reduction of 72 %. Similarly, hospitalization rates decreased from 44 % in the previous year to 6.7 % during treatment, equating to a reduction of 88 % ($p < 0.001$). Lung function and ICS use were also improved, with mean FEV_1 increasing by 4.9 % ($p = 0.023$) among 78 patients and the ICS dose decreasing by 30 % ($p < 0.001$).

5 Tolerability

5.1 General Profile

Overall, subcutaneous omalizumab was generally well tolerated in randomized clinical trials of adults, adolescents and children with severe persistent allergic asthma discussed in Sect. 4. Most adverse events were mild to moderate in severity, and the incidence was not significantly different between groups receiving add-on omalizumab or standard asthma therapy plus placebo [16, 23–28].

The most common treatment-related adverse event associated with omalizumab is transient injection-site reactions, including injection-site pain, bruising, swelling, erythema and pruritus [50, 51]. Other frequently reported adverse events include nasopharyngitis, headache and upper respiratory tract infection. A summary of the most common adverse events in placebo-controlled clinical trials is illustrated in Fig. 1.

In a systematic review (adults, adolescents and children; $n = 3429$) [50] and a pooled analysis (adults and adolescents; $n > 7,500$) [51] of clinical trial data (most patients had severe allergic asthma, but some trials were conducted in patients with moderate to severe disease), there was no significant difference between groups receiving add-on omalizumab or standard therapy with or without placebo in the incidence of serious or severe adverse events, or in the number of withdrawals due to adverse events, over treatment periods of up to 1 year. For example, in the systematic review of eight placebo-controlled trials, serious adverse events were reported in 3.8 % of patients in the omalizumab group compared with 5.3 % of patients in the placebo group [50]. The overall prevalence of treatment-related adverse events in this review was higher in the

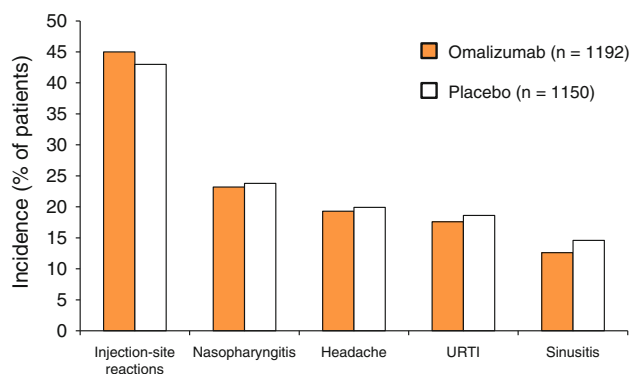


Fig. 1 Tolerability of add-on omalizumab in adults and adolescents with persistent allergic asthma. Results are from a review of data from several placebo-controlled trials of 16–32 weeks' duration, and include adverse events that occurred in >10 % of patients in either group [51]. Most patients had severe allergic asthma, but some studies were conducted in patients with moderate to severe disease. The omalizumab dose was based on body weight and pre-treatment total serum IgE levels. URT^I upper respiratory tract infection

omalizumab group than in control group (5.0 vs. 3.2 %; $p = 0.03$), largely as a result of a higher incidence of injection-site reactions (19.9 vs. 13.2 %; $p = 0.002$) [50].

A pooled analysis of clinical trial data in children, taken from two trials in patients ($n = 926$) with moderate to severe allergic asthma, demonstrate that the tolerability profile of omalizumab in children is generally similar to that of adults [52]. In the omalizumab and placebo groups, during treatment periods of up to 1 year, the most common adverse events were nasopharyngitis (24 vs. 23 %), upper respiratory tract infection (21 vs. 26 %), headache (21 vs. 20 %) and sinusitis (16 vs. 19 %), and the most common treatment-related events were headache (1.3 vs. 1.7 %), erythema (1.0 vs. 0.7 %) and urticaria (1.0 vs. 0.3 %) [52].

In the real-world setting (eXpeRience registry), 6.9 % (64 of 925) of omalizumab-treated patients (adults and adolescents) reported at least one serious adverse event over treatment periods of up to 2 years [31]. The most commonly reported serious adverse events were asthma (3.5 %), dyspnoea (0.8 %) and pneumonia (0.8 %). There was one case of anaphylaxis that was possibly due to omalizumab (Sect. 5.2). There were 25 serious adverse events that were thought to be due to omalizumab, the most common of which were dyspnoea, sudden chest tightness and headache (3 events each) [31]. Omalizumab was discontinued in five patients, and interrupted in two patients, as a result of a serious adverse event.

In children and adolescents ($n = 101$) treated with omalizumab for 1 year in the real-world setting, there were six serious adverse events that led to treatment withdrawal: urticaria ($n = 1$), anaphylaxis ($n = 1$), and systemic reactions including headache, fatigue, abdominal and muscular

pain ($n = 4$) [49]. Omalizumab was successfully reinstated in two patients [49].

5.2 Adverse Events of Special Interest

Hypersensitivity reactions to omalizumab, including anaphylaxis or urticaria are rare [3, 50]. Based on post-marketing use, the frequency of anaphylaxis associated with omalizumab is thought to be in the vicinity of 0.09–0.2 % [53]. In a systematic review of placebo-controlled studies in adults, adolescents and children, there were two reported cases of anaphylactic reactions in the omalizumab group ($n = 1,883$) and one case in the placebo group ($n = 1,546$); the difference between groups was not statistically significant [50]. The incidence of urticaria was 2.5 % in the omalizumab group and 2.1 % in the placebo group.

In an analysis of pooled data including 7,789 omalizumab-treated patients in 67 phase I–IV clinical trials, there was no evidence of an association between omalizumab treatment and risk of malignancy [54]. This analysis is supported by recent results from the prospective observational EXCELS (Evaluating Clinical Effectiveness and Long-term safety in patients with moderate-to-Severe asthma) cohort study that evaluated the long-term safety of omalizumab in patients (aged ≥ 12 years) with moderate to severe asthma (reported in an abstract) [55]. After a 5-year follow-up, the incidence of malignancy was similar in omalizumab- ($n = 5,007$) and non-omalizumab-treated ($n = 2,829$) patients.

Rare cases of Churg–Strauss syndrome (CSS) or hypereosinophilic syndrome have occurred in patients receiving anti-asthma medications, including omalizumab [3]. These events are associated with a reduction in oral corticosteroid therapy, and omalizumab treatment may unmask CSS in asthma patients being weaned from corticosteroids [56].

Omalizumab was associated with a higher than expected number of reports of arterial thrombotic events, including myocardial infarction, stroke, unstable angina and cardiovascular death, in a review of reports of arterial thrombotic events in asthmatic patients submitted to the US FDA from 2004–2011 [57]. Among asthma medications in this analysis, omalizumab had the second-greatest risk of arterial thrombotic events, after ICS. However, in a multivariate analysis of observational data controlling for baseline cardiovascular risk factors reported in the SPC, omalizumab was not associated with a risk for arterial thrombotic events (hazard ratio 1.11; 95 % CI 0.70–1.76) [3].

6 Pharmacoeconomic Considerations

This section summarizes recent (i.e. within the past 5 years) analyses on the use of add-on omalizumab in

patients with inadequately controlled severe allergic asthma. Cost–utility studies include the recent analysis in the National Institute for Health and Clinical Excellence (NICE) guidance in the UK [58], and an analysis based on observational data in the real-world setting [59]. Modelled pharmacoeconomic analyses of omalizumab, as with all such analyses, are subject to limitations, with the potential for input data to differ from real-life situations. Furthermore, results of pharmacoeconomic analyses in one country may not be applicable to other geographical regions because of differences in healthcare systems, medical practice and unit costs.

In cost–utility analyses, add-on omalizumab was cost effective compared with standard asthma therapy, with incremental costs per quality-adjusted life-year (QALY) gained falling within generally accepted willingness-to-pay thresholds [58, 59]. In the recent technology appraisal guidance from NICE, the assessment committee calculated an incremental cost-effectiveness ratio (ICER) of £23,200 per QALY gained compared with standard therapy for the combined population of adults, adolescents and children who had received frequent maintenance courses (≥ 4) of oral corticosteroids in the year prior to commencing omalizumab provided that discounting via a patient access scheme was incorporated [58]. The model used the perspective of the National Health Service and included administration and patient monitoring costs. Clinical data were taken from randomized, controlled trials. Costs and outcomes were modelled over a life time horizon, using annual discounting of 3.5 % and an omalizumab treatment duration of 10 years. Based on these cost–utility results, the NICE technology appraisal committee recommends add-on omalizumab as an option for treating severe persistent confirmed allergic IgE-mediated asthma in patients aged ≥ 6 years who need frequent oral corticosteroids and if omalizumab is made available on a patient access scheme. The committee acknowledged the benefits of omalizumab in reducing dependence on oral corticosteroids, which had not been captured in previous NICE pharmacoeconomic analyses [58].

Using a validated Markov model based on real-world data from the eXpeRience registry (Sect. 4.1.2.1), the incremental cost per QALY gained with add-on omalizumab versus standard therapy in The Netherlands was €38,371 (year of costing 2010) [59]. Patient and healthcare resource use data during 1 year of omalizumab treatment were compared with data for the year prior to commencing omalizumab when patients received standard care for severe allergic asthma. The analysis was conducted from the perspective of general medical practice, although societal costs based on prospectively assessed work days lost were included. The model had a

lifetime horizon, and discounted future outcomes at 1.5 % and future costs at 4 % [59]. In the base case analysis, patients treated with omalizumab gained more QALYs than patients in the standard care group as a result of a lower incidence of clinically significant or clinically significant severe asthma exacerbations. The main driver of costs was the cost of omalizumab therapy. Sensitivity analyses evaluated a range of variables, with ICERs per QALY gained ranging from €14,504–€80,332. The highest ICER was calculated when the model excluded mortality related to clinically significant severe asthma exacerbations, and the lowest ICER was calculated when the number of work days lost in retrospective data was applied to the standard care group. Variations in the duration of the model indicated that shorter-timeframes, such as 5 years, are associated with higher ICERs [59].

Two Italian retrospective analyses from the perspective of the Regional Health System calculated generally similar results with incremental costs per QALY gained of €25,983 (year of costing 2008) when omalizumab was added to standard therapy for 1 year [60], and €23,880 (year of costing 2011) when add-on omalizumab was administered for 3 years [61]. Both of these analyses used large databases to identify patients aged ≥ 12 years ($n = 23$ [60] and 16 [61]) who had received add-on omalizumab for the required observation period and had at least 12 months of clinical history preceding the start of omalizumab so that comparisons of clinical outcomes and healthcare consumption could be made [60, 61].

Further analyses in the real-world setting have demonstrated that omalizumab is associated with markedly reduced healthcare resource use [31, 32, 62]. In the UK real-world APEX study (Sect. 4.1.2.2), emergency room visits, hospitalizations and hospital bed days were all significantly ($p < 0.001$) reduced in the 12 months following omalizumab initiation compared with the period prior to omalizumab [32]. Similarly, data from the eXpeRience registry demonstrate substantial reductions in healthcare utilization (Table 3). Furthermore, the mean number of missed work days due to asthma per year decreased from 26.4 pre-treatment to 3.5 and 1.0 at months 12 and 24 months, respectively [31]. A similar pattern was observed for missed school days due to asthma, which decreased from 20.7 pre-treatment to 1.6 and 1.9, respectively.

Results from an observational, retrospective cohort study in Ireland suggest a cost saving of €834 per patient with severe allergic asthma treated with omalizumab for 6 months, compared with the 6 months prior to omalizumab, as a result of significant ($p < 0.001$) reductions in the number of hospital bed days and hospitalizations, and in the use of oral corticosteroids [62].

7 Dosage and Administration

In the EU, omalizumab added to ICS therapy is indicated for the treatment of adults, adolescents and children (aged ≥ 6 years) with severe persistent allergic asthma who have a positive skin prick test or in vitro reactivity to a perennial aeroallergen [3]. Patients must also experience frequent day-time symptoms or night-time awakenings, and have a history of multiple documented severe asthma exacerbations despite high doses of daily ICS plus a LABA. A further proviso for omalizumab treatment in adults and adolescents, but not children, is evidence of reduced lung function ($FEV_1 < 80\%$).

Omalizumab is administered via subcutaneous injection, and the dose and frequency of administration (i.e. every 2 or 4 weeks) is determined according to baseline IgE (IU/mL; determined by any commercial serum total IgE assay) and body weight (kg) [3]. The baseline total serum IgE level for eligibility for omalizumab in the EU ranges from 30–1,500 IU/mL. Depending on IgE levels and body weight, a 75–600 mg dose of omalizumab via 1–4 injections should be given at each administration. Dose determination charts and a chart converting dose to injection number and volume are available in the prescribing information [3]. The maximum recommended dose of omalizumab is 600 mg every 2 weeks. Clinical use has shown that patients with IgE levels < 76 IU/mL are less likely to benefit from treatment. Prior to omalizumab therapy in adults and adolescents with IgE levels < 76 IU/mL or children with IgE levels < 200 IU/mL, unequivocal in vitro reactivity to a perennial allergen should be confirmed. Patients with baseline IgE levels or body weights that are outside the limits of the dose table should not receive omalizumab [3].

Omalizumab is intended for long-term use [3]. Clinical studies have demonstrated that the efficacy of omalizumab is generally not evident until after 12–16 weeks of therapy [3]. After 16 weeks of treatment (and at subsequent time points), the decision to continue omalizumab should be made by the physician based on their overall assessment of effectiveness. Quantifying free serum IgE as a means of confirming omalizumab's efficacy in order to guide continued dosing has not been possible as commercially available assays recognize both free IgE and omalizumab-bound IgE. However, a new recovery-enzyme linked immune sorbent assay (R-ELISA) can now quantify both the antigen (free IgE) and the therapeutic antibody (omalizumab) [63]. Serum total IgE levels, which are elevated during treatment, can remain elevated for up to 1 year after discontinuing omalizumab and, therefore, should not be used to calculate dosage requirements after lapses in treatment of < 12 months [3].

Anaphylactic reactions can occur in patients treated with omalizumab (Sect. 5.2), and medicines used for the treatment of anaphylaxis should be on hand following omalizumab administration. Local prescribing information should be consulted for additional information regarding dosages, warnings, contraindications and precautions.

8 Place of Omalizumab in the Management of Patients with Severe Persistent Allergic Asthma

Asthma treatment guidelines recommend a stepwise approach to therapy, with the aim of achieving and maintaining symptom control by stepping treatment up or down as necessary [1]. GINA guidelines recommend that add-on anti-IgE treatment with omalizumab is considered in patients with persistent allergic asthma that remains uncontrolled despite step 4 treatment (Sect. 1) [1].

The therapeutic efficacy of omalizumab primarily results from a reduction in free serum IgE levels and eosinophils, thereby inhibiting the cascade of inflammatory mediators and associated symptoms in susceptible patients (Sect. 2).

Add-on omalizumab significantly reduced the asthma exacerbation rate (primary endpoint) compared with placebo in well designed clinical trials in adults and adolescents (Sect. 4.1.1.1) and children (Sect. 4.2) with severe persistent allergic asthma. Furthermore, add-on omalizumab reduced the need for ICS in adults and adolescents, and improved asthma control and symptoms and asthma-related QOL in all age groups. The efficacy of omalizumab was also demonstrated in the real-world setting, with large observational studies of up to 2 years duration demonstrating that add-on therapy leads to reduced rates of hospitalizations, emergency room visits and unscheduled doctor's visits, as well as improvements in asthma symptom scores and physician-assessed GETE (Sects. 4.1.2 and 4.2).

The extent to which free serum IgE is reduced is dependent on the omalizumab dose, the body weight of the patient and their baseline total serum IgE level (Sect. 7). Tiered dosing tables are available for establishing individualized treatment regimens to ensure that patients receive a dose of at least 0.016 mg/kg/IgE (IU/mL) every 4 weeks [3].

Overall, omalizumab was well tolerated in clinical trials (Sect. 5.1). Most adverse events were mild to moderate in severity, and the most common event was transient injection-site reactions. The tolerability profile in children was generally similar to that observed in adults and adolescents. Anaphylaxis is rare, but patients should be monitored closely after drug administration (Sect. 7). Further tolerability data on the long-term use of omalizumab are needed.

Results of clinical trials demonstrate that not all patients respond to omalizumab despite careful selection based on recent guidelines [1]. Predicting which patients with severe allergic asthma are most likely to respond to omalizumab is difficult based on pre-treatment characteristics [41]. Although omalizumab effectively reduces free serum IgE levels, a correlation between free serum IgE and treatment response has not been identified (Sect. 2.2) and, thus, the reduction in free serum IgE levels is not sufficient to predict response [19].

The heterogeneity of asthma and patterns of allergic airway inflammation are likely to contribute to variations in response to asthma medications. Various phenotype clustering approaches have been used in an attempt to characterize asthma heterogeneity, which may have implications for future treatment. Results of a retrospective analysis using data from the randomized EXTRA trial [16], suggest that baseline levels of biomarkers of Th2 inflammation may potentially have a role in identifying patients most likely to benefit from omalizumab treatment (Sect. 2).

To date, the most accurate method of predicting a continuing beneficial response to omalizumab is via the physician's overall assessment of response after 16 weeks (Sect. 4.1.1.5) [41], at which time, those who are considered to have achieved a marked improvement in overall asthma control should continue with treatment [3].

Omalizumab is intended to be administered over the long-term; however, recent evidence suggests that indefinite treatment may not be required as IgE production tends to decrease over time during therapy (Sect. 2.2). Furthermore, in a small trial in patients with severe cat allergen-induced asthma, asthma symptoms remained relatively well controlled 3 years after completing 6 years of omalizumab treatment [64]. More data are needed to determine the optimum treatment duration.

The costs associated with asthma, and severe asthma in particular, place a substantial economic burden on health-care providers [65]. Add-on omalizumab was cost-effective compared with standard therapy in cost-utility analyses modelled on randomized trials and on real-world data over a life-time horizon, with ICERs falling within generally accepted willingness-to-pay thresholds (Sect. 6). Not surprisingly, the main driver of costs was the purchase price of omalizumab; however, the lower incidence of clinically significant or severe asthma exacerbations, the reduction in the use of oral corticosteroids and the improvement in HR-QOL were important factors in reducing costs. Evidence also suggests that cost utility increases as the duration of treatment increases.

Omalizumab is currently being evaluated for the treatment of various other allergic conditions, including allergic rhinitis and urticaria; results of clinical trials are awaited with interest [66]. Furthermore, recent evidence in a small

proof-of-concept trial suggests that omalizumab may also have a therapeutic role in severe non-allergic asthma [67].

In conclusion, add-on omalizumab is an effective and well tolerated agent in adults, adolescents and children aged ≥ 6 years with severe persistent allergic asthma that is poorly controlled with medium- to high-dose ICS and a LABA. Immunological factors do not predict a response to omalizumab, and the best predictor of a continued response is the physician's overall assessment after 16 weeks of therapy. The optimum duration of therapy has not been determined, and currently the duration is at the discretion of the treating physician. Cost-utility studies suggest that omalizumab is cost effective compared with standard therapy over a life-time horizon. Thus, in difficult-to-treat patients with severe persistent allergic asthma, omalizumab provides a valuable treatment option.

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