Primary Care Respiratory Journal (2008); 17(2): 62-72

Primary Care RESPIRATORY JOURNAL
www.thepcrj.org

REVIEW

The use of omalizumab in asthma

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Received 7th June 2007; revised version received 1st February 2008; accepted 3rd March 2008

Abstract

Asthma causes a substantial burden of morbidity and mortality, affecting 300 million people worldwide – a figure predicted to increase to 400 million by 2025. Despite the availability of a variety of treatment options and detailed treatment guidelines, many patients with asthma, and in particular those with severe persistent asthma, remain inadequately controlled. Approximately 50–80% of severe asthma has an allergic component, with immunoglobulin E (IgE) playing a role in the underlying allergic inflammatory cascade. Omalizumab is a humanised monoclonal anti-IgE antibody that targets IgE and partially inhibits the inflammatory cascade. Clinical trials have demonstrated that omalizumab added to standard asthma therapy reduces exacerbations and emergency visits with concomitant improvements in asthma control and quality of life in patients with moderate-to-severe and severe persistent allergic (IgE-mediated) asthma. Add-on omalizumab is indicated for the treatment of patients with inadequately controlled moderate-to-severe (US label) and severe (EU label) persistent allergic asthma despite treatment with high-dose inhaled corticosteroids (and in the EU, high-dose inhaled corticosteroids plus a long-acting β_2-agonist). Within this highly-targeted patient population, analyses have been unable to identify pre-treatment clinical characteristics that are predictive of a greater response to omalizumab. In contrast, assessment of response to omalizumab following 16 weeks of treatment appears to be reliably judged by physicians in clinical trial settings and may be a feasible means of selecting patients who should continue treatment.

D Price. *Prim Care Resp J* 2008; **17**(2): 62-72.
doi:10.3132/pcrj.2008.00031

Keywords omalizumab, asthma, anti-IgE, immunoglobulin-E, review

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Introduction

Asthma affects approximately 300 million people worldwide and this figure is predicted to rise to 400 million by 2025.[1] Asthma mortality remains stubbornly high, with the World Health Organization (WHO) estimating 255,000 deaths from asthma in 2005.[2] In addition, asthma causes a high burden of disability, with a similar magnitude to osteoarthritis, cirrhosis, diabetes and schizophrenia.[1,2] In the UK, the asthma mortality rate has declined slightly over the last 20 years, although it would be beneficial to see this reduced even further.[3] In 2005 the asthma mortality rate in the UK was calculated to be 22/1,000,000[4] which, assuming the total population to be

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around 60 million, equates to approximately 1,320 deaths/year.

The symptoms of asthma can vary considerably, ranging from mild to severe, both between patients and at different times within the same patient. The International Primary Care Respiratory Group (IPCRG) guidelines classify asthma severity into four steps (intermittent, mild persistent, moderate persistent or severe persistent) according to clinical features before treatment, as well as by the daily medication regimen and the response to treatment.[5] However, patients at the severe end of the spectrum who remain symptomatic, despite receiving best available treatment and optimal management efforts, often have limited therapeutic options. These patients are at a high risk of serious morbidity and mortality and represent the sector of the asthma population today with the greatest unmet medical need and healthcare utilisation.[6,7,8] A recently published study allowed assessment of the impact of asthma exacerbations on health-related quality of life (QoL) in patients with moderate-to-severe asthma. Both disease-specific and generic QoL instruments were dramatically poorer for patients with exacerbations than those without ($p<0.001$).[9] Despite advances in our understanding of the inflammatory basis of asthma and a growing acceptance of disease management guidelines, inadequate control of asthma remains a serious problem for both patients and physicians.

The Global Initiative for Asthma (GINA) guideline defines asthma as a chronic inflammatory disorder of the airways.[7] This inflammation is worsened in those with allergic asthma by reactions to a wide variety of aeroallergens and leads to the characteristic symptoms of asthma. A large proportion of patients with severe asthma also display symptoms of allergic asthma; the European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) study showed that around 50% of patients with severe asthma had positive reactions to skin prick tests for common aeroallergens,[10] while The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study showed the figure to be around 80%.[11]

Immunoglobulin E (IgE) is recognised as an important mediator of allergic reactions thought to be partially responsible for the induction and maintenance of chronic airway inflammation and asthma-related symptoms.[12] In patients with allergic asthma who are sensitive to a particular allergen, exposure to the allergen causes an early-phase and late-phase asthmatic response. The early-phase response occurs within minutes of allergen exposure following its binding to IgE attached to IgE receptors on inflammatory cells (mast cells), which stimulates the rapid release of inflammatory molecules such as histamine, prostaglandin, leukotrienes and cytokines. These inflammatory molecules may worsen the symptoms of asthma by stimulating contraction of airway smooth muscle and increasing mucus production. This leads to asthmatic symptoms such as wheezing, coughing, chest tightness and shortness of breath. Release of cytokines from mast cells and other inflammatory cells attracts eosinophils to the site of inflammation, which release a variety of other inflammatory molecules that can damage tissues and cause the characteristic late-phase asthmatic responses such as bronchoconstriction.

Omalizumab is a recombinant, humanised monoclonal antibody and is the first treatment to target IgE, inhibiting the IgE-mediated asthma inflammatory cascade before it starts. The aim of this review is to evaluate the clinical profile of omalizumab based on data from phase III clinical studies in adult and adolescent patients with allergic asthma, and to consider the potential role of omalizumab in the management of patients with severe persistent allergic (IgE-mediated) asthma who remain symptomatic despite therapy. Severe persistent asthma has been defined by GINA guidelines as asthma patients with reduced lung function (forced expiratory volume in one second [FEV_1] or peak expiratory flow [PEF] $\leq$60% predicted; PEF or FEV_1 variability > 30%) who experience daily symptoms together with frequent exacerbations despite appropriate asthma therapy.[7]

Severe asthma often remains symptomatic despite high dose inhaled corticosteroids and long-acting β_2-agonists

The IPCRG guidelines[5] recommend that treatment should be tailored to asthma severity, with defined regimens for each treatment step. For example, patients with intermittent asthma should receive a rapid-acting inhaled β_2-agonist while those with mild persistent asthma should also receive a low-dose inhaled corticosteroid (ICS). For patients with moderate or severe asthma an inhaled long-acting β_2-agonist (LABA) or a leukotriene antagonist (LTRA) may be added as well as additional controller medication. The GINA 2007 guideline[7] recommends that treatment decisions are based on the patient's current level of asthma control and current medication. The IPCRG and GINA goals for asthma management are similar and both include the prevention of asthma exacerbations/need for emergency care, the prevention of symptoms, and improvements in daily activities.[5,7]

Despite guideline-based asthma management goals, the Asthma Insights and Reality in Europe (AIRE) study of 2,803 European patients showed that 46% of patients reported daytime symptoms, 30% had asthma-related sleep disturbances at least once a week, 25% had an unscheduled urgent care visit in the past year, 10% had an emergency room (ER) visit, and 7% had an overnight hospitalisation.[13] Extending this survey to include 7,786 adults and 3,153 children with asthma in Europe, North America and Asia

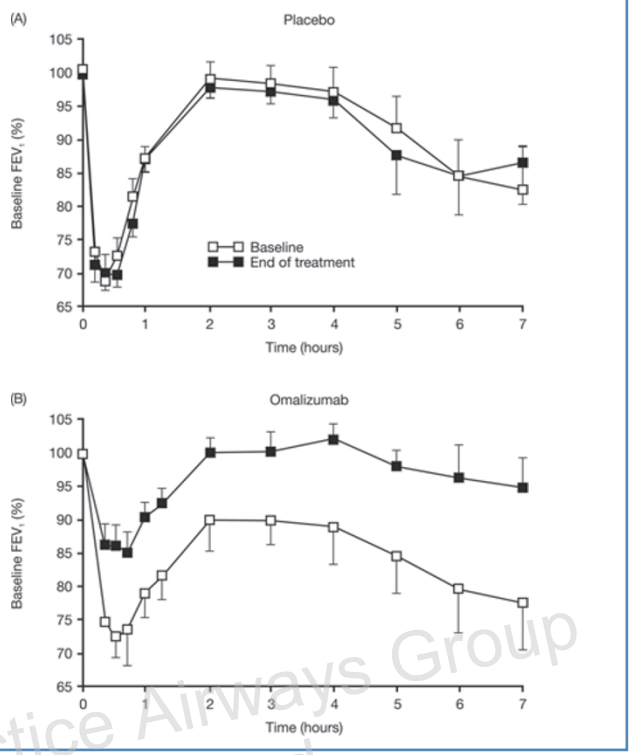
confirmed the findings of the AIRE study.[14] The GINA goal of minimal chronic symptoms was not met in a large percentage of patients, with 45–84% of patients having daytime symptoms and 33–70% having night-time awakenings during the previous four weeks. In addition, many patients did not meet the goal of minimal exacerbations and no emergency visits, with 9–31% having hospital admissions due to asthma. In addition, a European survey of 1,300 patients with severe asthma found that approximately 50% of patients felt that they were not achieving GINA treatment goals.[15] These studies suggest that asthma is often poorly controlled and that levels of control do not meet IPCRG or GINA treatment goals.

There are many factors that may lead to inadequate asthma control, including poor inhaler technique[16] and poor adherence to medication.[17] Patients with asthma who smoke are at increased risk of asthma-related mortality and experience an accelerated decline in pulmonary function.[18–21] Smokers with mild persistent asthma have also shown insensitivity to ICS treatment, particularly at low doses,[22,23] although the same population showed greater improvements with LTRAs[23] than non-smokers.

Studies have also shown that patients with asthma and physician-diagnosed concomitant allergic rhinitis experience significantly more asthma-related hospitalisations, visit a physician more frequently, and incur higher asthma-related drug costs compared with patients with asthma alone.[24–26] Co-existing gastro-oesophageal reflux disease,[27] sinusitis,[28] stress,[29,30] and sleep apnoea[31] may also influence the level of asthma control. In addition, patients with severe asthma may be prone to anxiety and depression[32,33] that can worsen non-adherence to medication regimens and lead to poorer asthma control.

In many cases inadequate asthma control is due to the underuse of controller medications,[13,14] but studies have also shown that many patients have inadequate asthma control despite high-dose ICS and additional asthma controller therapy. The Gaining Optimal Asthma Control (GOAL) study, for example, investigated whether treatment with fluticasone propionate or salmeterol/fluticasone combination therapy could achieve guideline-based asthma control in patients with uncontrolled asthma.[34] In patients with the most severe asthma, 38% remained inadequately controlled despite optimised treatment with salmeterol/fluticasone. When a course of oral steroids was added to the highest recommended dose of salmeterol/fluticasone at the end of this one-year study, only a further 7% of patients had well-controlled asthma, i.e. 31% remained inadequately controlled. Another study, examining the attitudes and actions of 3,145 physician-recruited patients (≥16 years) with asthma who were receiving regular maintenance therapy with ICS (30% of patients) or ICS plus LABA (70% of patients), found that 52% of patients were classified by the Asthma Control Questionnaire (ACQ) as having uncontrolled asthma and 74% of patients used short-acting β_2-agonists daily.[35] Moreover, 55% of patients with uncontrolled asthma according to the ACQ classed their asthma control as 'relatively good'.

Figure 1. Omalizumab inhibits both the early and late asthmatic response.[46]



Anti-IgE therapy

Omalizumab is the first of a new class of agents designed to target IgE and interrupt the allergic inflammatory cascade[36–38] at an early stage. Omalizumab binds to the Cε3 domain of all forms of circulating IgE, regardless of allergen specificity, and prevents IgE binding to its receptors on mast cells/basophils and the subsequent IgE-mediated responses.[39] Once omalizumab has bound to free IgE, it forms small complexes (trimers or hexamers) that are then cleared from the circulation via interactions with FcγRs of the hepatic sinusoidal endothelial cells of the reticuloendothelial system.[40,41] As IgE upregulates IgE receptors on mast cells,[42] the reduction in the amount of free IgE in the circulation also results in a decrease in the number of IgE receptors on the surface of mast cells.[12,43,44]

Early studies showed that omalizumab reduced both the early and late asthmatic responses.[45,46] In one study,[46] the effects of omalizumab on early and late phase asthmatic responses to allergen were assessed by measuring mean

maximal decreases in FEV_1 within 1 hour (early response) or 2–7 hours (late response) in a study of 19 patients with mild allergic asthma after nine weeks of omalizumab treatment. The early asthmatic response was reduced by 85% (p=0.01) and the late asthmatic response by slightly more than 65% (p=0.047) compared with placebo (Figure 1). In addition, omalizumab significantly reduced eosinophil numbers in airway tissue and induced sputum in a study of 45 patients with corticosteroid-naive mild or moderate asthma.[47] After 16 weeks of treatment with omalizumab or placebo, there were significant changes from baseline in several cell types in the bronchial submucosa of patients who received omalizumab. In the omalizumab group, the percentage of eosinophils in induced sputum decreased from 4.8% to 0.6% (p=0.05 vs placebo) and there was a significant reduction in tissue eosinophils in the bronchial submucosa from 8.0 to 1.5 cells/mm^2 (p=0.03 vs placebo).[47]

Indication

As of April 2007, omalizumab is approved for the treatment of asthma in 53 countries with slight variations in the precise indication. In the European Union, omalizumab was approved in 2005 as add-on therapy to improve asthma control in adult and adolescent patients (≥12 years) with severe persistent allergic (IgE-mediated) asthma who have the following characteristics: a positive skin test or serum IgE to a perennial aeroallergen; reduced lung function (FEV_1 <80%); frequent daytime symptoms (cough, wheeze, breathlessness, shortness of breath, chest tightness) or night-time awakenings; and multiple documented severe asthma exacerbations (PEF/FEV_1 <60% of patients' maximum recorded) despite receiving daily high-dose ICS plus a LABA. 'Multiple severe asthma exacerbations' is defined as either two or more severe exacerbations of asthma requiring hospital admission within the previous year, or three or more severe exacerbations of asthma within the previous year, at least one of which required admission to hospital.

Omalizumab has recently (October 2007) been accepted by the Scottish Medicines Consortium (SMC) for use within NHS Scotland as add-on therapy to improve asthma control in adult and adolescent patients (≥12 years) with severe persistent allergic asthma. The SMC restricted the use of omalizumab to hospital physicians experienced in the diagnosis and treatment of severe persistent asthma and in patients who are currently prescribed oral corticosteroids and for whom all other therapy options have failed.[48]

Omalizumab was previously approved in the United States in 2003 for the treatment of patients with moderate-to-severe persistent allergic (IgE-mediated) asthma despite treatment with ICS. Other countries have tended to adopt similar indications when approving omalizumab. In all countries, omalizumab is indicated for patients with baseline

Figure 2. Omalizumab dosing tables. Doses (milligrams per dose) administered by subcutaneous injection for adults and adolescents (12 years of age and older) with asthma in the EU. The dosing table in the package inserts of the marketed product may differ slightly from the EU dosing table; physicians should consult the package insert for information on omalizumab dosing.

(A) Administration every 4 weeks

	Body weight (kg)									
Baseline IgE (IU/mL)	>20–25	>25–30	>30–40	>40–50	>50–60	>60–70	>70–80	>80–90	>90–125	>125–150
30–100	75	75	75	150	150	150	150	150	300	300
>100–200	150	150	150	300	300	300	300	300		
>200–300	150	150	225	300	300					
>300–400	225	225	300							
>400–500	225	300				Administration every 2 weeks: see Panel B				
>500–600	300	300								
>600–700	300									

(B) Administration every 2 weeks

	Body weight (kg)									
Baseline IgE (IU/mL)	>20–25	>25–30	>30–40	>40–50	>50–60	>60–70	>70–80	>80–90	>90–125	>125–150
30–100										
>100–200	Administration every 4 weeks: see Panel A								225	300
>200–300						225	225	225	300	375
>300–400				225	225	225	300	300		
>400–500			225	225	300	300	375	375		
>500–600			225	300	300	375	Do not administer – data are unavailable for dose recommendation			
>600–700		225	225	300	375					

total IgE 30–700 IU/mL and is administered every two or four weeks at a dose determined according to the patient's baseline IgE level and bodyweight using dosing tables (Figure 2).

Efficacy and tolerability in patients with severe allergic asthma

The efficacy of omalizumab has been investigated in a series of phase III clinical studies in patients (≥12 years of age) with predominantly severe allergic asthma[49–58] according to IPCRG guideline definitions. Five studies were randomised, double-blind, placebo-controlled trials in patients with moderate-to-severe or severe asthma,[49,51–56] and two were randomised open-label trials.[50,57] The patients included in these studies reflect the most common product monographs for omalizumab, (moderate-to-severe or severe allergic asthma). Between 88% and 100% of patients in these studies were classified as having severe persistent asthma. A summary of the trial designs and main outcomes is provided in Table 1 (see Appendix A at www.thepcrj.org). The efficacy of omalizumab was evaluated in two 28-week trials, both including a 16-week stable ICS phase and a 12-week ICS reduction phase (Table 1 at www.thepcrj.org).[52,54] The Busse study included subjects (n=525; 12–75 years) with severe allergic asthma who required daily ICS for symptom control; during the stable ICS phase, omalizumab treatment resulted in significantly fewer asthma exacerbations per subject (0.28 vs 0.54; p=0.006) and fewer patients experienced an exacerbation compared with placebo (14.6% vs 23.3%; p=0.009).[52] Omalizumab treatment during the ICS reduction phase resulted in reduced numbers of exacerbations per subject (0.39 vs 0.66, p=0.003) and a reduced number of subjects with exacerbations compared with placebo (21.3% vs 32.3%; p=0.004).[52] There was also a significant reduction in ICS dose in subjects treated with omalizumab compared with placebo (75% vs 50%; p<0.001).[52] The Solèr study enrolled patients with moderate-to-severe allergic asthma (n=546; ≥12 years) who remained symptomatic despite ICS (500–1,200 mcg/day beclomethasone dipropionate [BDP]).[54] Subjects were randomised to receive placebo or omalizumab subcutaneously every two or four weeks, with the dose based on body weight and total serum IgE. Doses ranged from 150 mg every four weeks to 375 mg every two weeks. Patients receiving omalizumab had 58% fewer exacerbations versus placebo during the stable ICS phase (p<0.001). During the steroid-reduction phase, 52% fewer exacerbations occurred in the omalizumab group versus the placebo group (p<0.001), despite a significantly greater reduction in BDP dose on omalizumab (p<0.001).[54] Following each study's ICS-reduction phase, patients could enter a 24-week double-blind extension phase, continuing their study treatment at the lowest sustainable dose of BDP. Results from both extension studies indicated that the use of omalizumab resulted in significantly lower numbers of exacerbations and exacerbations per patient compared with placebo (p<0.05) despite lower ICS doses (Table 1 at www.thepcrj.org).[53,55] Significant improvements in lung function, as measured by FEV_1, were observed with omalizumab therapy compared with placebo, after 32, 36, 40 and 44 weeks of extension-phase treatment,[53] although no consistent effect on lung function has been observed to date in the majority of clinical trials.

A retrospective pooled analysis of data from the seven trials was conducted using data from 4,308 patients, 93% of whom met GINA 2002 criteria for severe persistent asthma.[58] Add-on omalizumab reduced asthma exacerbation rates by 38% and total emergency visits by 47%, compared with control (Table 2). A separate pooled analysis assessed QoL in 1,221 patients receiving omalizumab and 1,032 receiving placebo/control in six clinical trials.[59] Asthma-related QoL was assessed using the Juniper Asthma Quality of Life Questionnaire (AQLQ).[60] This questionnaire consists of 32 questions grouped into four domains: activity limitations (11 questions), emotions (5), symptoms (12), and exposure to environmental stimuli (4). Each question was answered by the patient on a 7-point scale and a lower AQLQ score represented greater QoL impairment. Omalizumab improved QoL in all studies, delivering significantly greater improvements in AQLQ total score compared with placebo/control and in the proportion of patients in the pooled population recording a ≥0.5 point improvement in AQLQ total score (Table 2).

Patients with severe asthma are at increased risk of hospitalisation for exacerbations and asthma-related death.[61–64] The INNOVATE study was a randomised, placebo-controlled, double-blind study conducted in 419 patients with inadequately-controlled severe persistent allergic asthma despite treatment with high dose ICS plus LABA and additional controller medications as necessary, a patient population closely reflecting the EU label.[49] Among the patient inclusion criteria was a history of two clinically significant exacerbations (requiring systemic corticosteroids), or one severe exacerbation (PEF or FEV_1 <60% of personal best and requiring systemic corticosteroids) the previous year. Of these patients, 67% were considered to be at high risk of asthma-related death.[19,63] INNOVATE showed that adding omalizumab to high-dose ICS plus LABA resulted in a 26% reduction in the rate of clinically significant exacerbations (this figure included a post-hoc adjustment for baseline exacerbation history; the unadjusted result was of a similar magnitude but failed to reach statistical significance), a 50% reduction in the rate of severe exacerbations, and a 44% reduction in total emergency visits (hospital admissions, ER visits and unscheduled doctor visits) (Figure 3; Table 3), compared with

Table 2. Pooled analysis: reductions in exacerbations and emergency visits[58] and increased quality of life[59] with omalizumab.

	Omalizumab (n=2,511)	Control (n=1,797)	Difference (%)	Ratio (95% CI)	p-value
Exacerbation rate*	0.91	1.47	38%	0.617 (0.535–0.712)	<0.001
Total emergency visit rate*	0.33	0.62	47%	0.533 (0.401–0.709)	<0.001
AQLQ (change from baseline, LSM)	(n=1,221)	(n=1,032)			
Overall	1.01	0.61	-		<0.001
Activity	1.03	0.65	-		<0.001
Emotions	1.04	0.62	-		<0.001
Symptoms	0.97	0.54	-		<0.001
Environment	1.01	0.60	-		<0.001

*Annualised; AQLQ = Asthma Quality of Life Questionnaire

placebo. The INNOVATE study also found that add-on omalizumab treatment provided significant QoL improvements (Figure 4). Compared with placebo, 27% more patients receiving omalizumab achieved clinically meaningful improvements in QoL, equating to a ≥0.5 point improvement from baseline in AQLQ total score measured across the domains of activity, limitations, asthma symptoms, emotional function and environmental exposure (Table 3).

The observed steroid-sparing effects of omalizumab are important for severe persistent allergic asthmatics due to the deleterious effects of daily high-dose ICS or oral corticosteroids. Omalizumab has proved useful as an adjunctive treatment to ICS therapy; however, it will be important to determine its clinical effectiveness in comparison with alternative treatments such as LABAs, anti-leukotriene agents or phosphodiesterase inhibitors. Studies directly

Figure 3. Omalizumab significantly reduced severe exacerbations and total emergency visits in the INNOVATE study.[49]

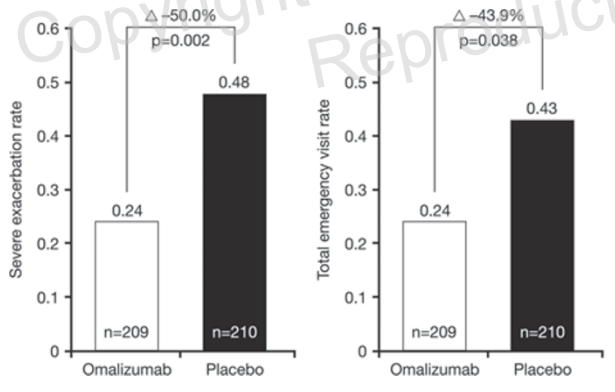


Figure 4. Change in asthma-related quality of life (AQLQ) scores from baseline in the INNOVATE study.[49] LSM = least squares mean.

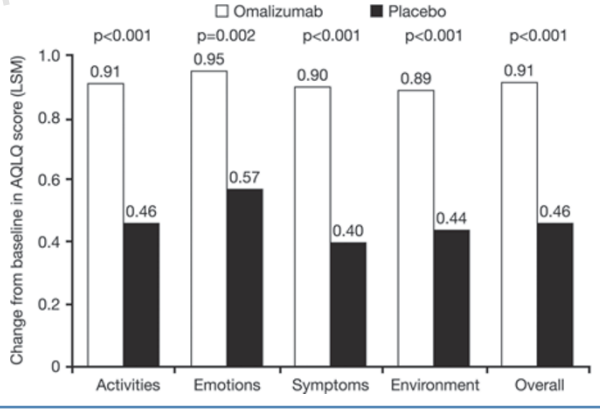


Table 3. INNOVATE: reductions in exacerbations and emergency visits and increased quality of life with omalizumab.[49]

	Omalizumab (n=209)	Placebo (n=210)	Difference (%)	p-value
Clinically significant asthma exacerbation (rate)	0.68	0.91	26%	0.042
Severe asthma exacerbation (rate)	0.24	0.48	50%	0.002
Total emergency visits (rate)	0.24	0.43	44%	0.038
QoL, improvement from baseline, n (%)				
≥0.5	124 (60.8)	98 (47.8)	-	0.008
≥1.0	92 (45.1)	51 (24.9)	-	<0.001
≥1.5	56 (27.5)	35 (17.1)	-	0.011

comparing the efficacy of omalizumab against these alternative therapies have yet to be performed.

The efficacy of omalizumab has also been evaluated in a 28-week double-blind, randomised, placebo-controlled trial in children (n=334; 6–12 years) with moderate-to-severe allergic asthma dependent on ICS.[65] During a run-in phase, all children were switched to equivalent doses of BDP, and the dose was adjusted to ensure asthma control was achieved. Children were randomised to subcutaneously administered placebo (n=109) or omalizumab (n=225) at a dose based on body weight and initial serum IgE. The BDP dose was initially maintained for 16 weeks (stable-steroid phase), then reduced over the subsequent eight weeks to the minimum effective dose (steroid-reduction phase) and then kept constant for the final four weeks. More patients on omalizumab therapy significantly decreased their ICS dose and by greater amounts than those on placebo (median reduction 100% vs 66.7%; p=0.001). BDP was withdrawn completely in 55% of patients administered omalizumab compared with 39% in the placebo group (p=0.004). During the steroid-reduction phase significantly fewer subjects in the omalizumab group had asthma exacerbation episodes (18.2% vs 38.5%; p<0.001), and the mean number of episodes per patient was lower than with placebo (0.42 vs 2.72; p<0.001).

Studies of omalizumab have shown that treatment is generally well tolerated. The frequency and severity profile of adverse events in omalizumab recipients was similar to that seen in patients receiving placebo or best available therapy.[66] The most commonly reported adverse events were injection site reactions – including injection site pain, swelling, erythema and pruritus – and headaches, and the vast majority were mild or moderate in severity. The overall observed incidence rate of malignancy following omalizumab therapy was comparable to that reported in the general population. IgE may be involved in the immunological response to some helminth infections and in patients at high risk of helminth infection, a placebo-controlled trial showed a slight increase in infection rate with omalizumab.[67] The helminth infection rate in the overall clinical programme, which was not designed to detect such infections, was observed to be rare (<1 in 1,000 patients). However, caution may be necessary in patients at high risk of helminth infection, in particular when visiting areas where helminthic infections are endemic.

As omalizumab is a protein, it might be expected to be associated with hypersensitivity reactions and related immunological effects. However, as residues of murine origin constitute less than 5% of the omalizumab molecule and omalizumab cannot cross-link FcεRI receptors and activate effector cells, omalizumab has low anaphylactogenic potential. In phase II and phase III clinical trials the incidence of anaphylactic response was 0.14% in omalizumab-treated patients and 0.07% in control patients.[68] Most of these reactions occurred within two hours after the first injection of omalizumab, but some started beyond two hours and occasionally beyond 24 hours after the initial injection. Patients should be informed that such reactions are possible, and medications for the treatment of anaphylactic reactions should always be available for immediate use following administration of omalizumab. The Omalizumab Joint Task Force of the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma and Immunology Executive Committees has recommended that patients be kept under observation for 30 minutes after each injection. This time should be extended to two hours for the first three injections. However, this could be modified based on a physician's clinical judgment after discussing risks with the patient. Patients should also be prescribed and educated on the proper use of the epinephrine autoinjector and advised to carry this before omalizumab administration and for the next 24 hours after omalizumab administration.[69] The US Food and Drug Administration (FDA) has recently requested the addition of a boxed warning to the product label, based on the incidence of anaphylactic reactions from post-marketing surveillance (0.1% incidence, source: FDA website). At the time of writing, discussions between the manufacturers of omalizumab and the FDA and the European Committee for Medicinal Products for Human Use (CHMP) are ongoing.

Identifying patients who may benefit from add-on omalizumab therapy

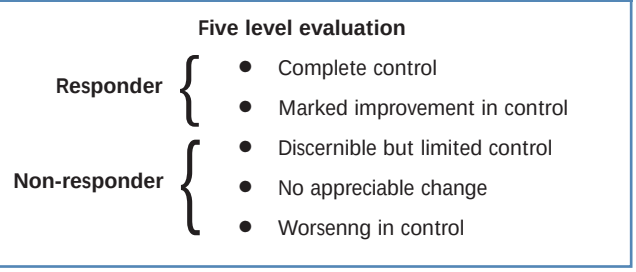
Assessing response

Analyses of data from studies of omalizumab have shown that it is difficult to predict which patients within the label population derive the greatest benefit from omalizumab based on pre-treatment demographic and clinical characteristics.[70] Alternative approaches to identify patients who respond to omalizumab following a course of therapy have therefore been studied.[70] Response criteria evaluated were: physician's overall assessment, a composite measure that encompasses multiple aspects of response including patient interviews, review of medical notes, spirometry and diaries of symptoms, rescue medication use and peak expiratory flow (complete control of asthma or marked improvement on a 5-level evaluation: Figure 5); ≥0.5 point improvement in total AQLQ score; ≥200 mL improvement in FEV_1; ≥1.0 point reduction in daytime symptom score (4-point scale: 0=no symptoms, 4=major discomfort); ≥1.0 point reduction in nocturnal symptom score (4-point scale: 0=no symptoms, 4=major discomfort); and reduction ≥1/week and by at least 50% in night awakenings.

Identifying responders

Physician's overall assessment and AQLQ were able to identify

Figure 5. Physician's overall assessment of treatment response.



a greater proportion of responders in the INNOVATE study (61% of omalizumab-treated patients as responders) compared with single item measures (18–32% of patients), whilst maintaining a similar discrimination for exacerbation outcomes (asthma worsening requiring systemic corticosteroids) (Table 4).[70] Physician's overall assessment was also able to discriminate for severe asthma exacerbations (FEV_1 or peak expiratory flow [PEF] < 60% of personal best and requiring systemic corticosteroids), whereas severe exacerbation rate was similar in both responders and non-responders according to AQLQ.[70] Based on these data, the physician's overall assessment, during clinical trials, appears to be the best method of evaluating response to omalizumab and includes degree of asthma control, QoL, control of exacerbations, avoidance of unscheduled healthcare utilisation, spirometry and PEF measures, and a global evaluation of treatment effectiveness. Patients identified as responders according to the physician's overall assessment had greater benefits across a range of measures of asthma control (Table 5). Omalizumab add-on therapy should be initiated and monitored by a physician experienced in both allergy and respiratory medicine in a specialist centre.

Currently there is no universal clinical description of a responder to omalizumab. In assessing response to asthma treatment, failure to meet threshold-based criteria does not necessarily reflect a smaller treatment benefit, but may reflect a more severe, less well-controlled patient population prior to treatment. Broad markers of asthma control that measure a range of outcomes can provide meaningful information on patients' asthma control and response to treatment.[71,72]

In the responder population of the INNOVATE study, rates of clinically significant exacerbations were reduced by 60% (0.39 vs 0.99, p<0.001), severe exacerbations by 76% (0.13 vs 0.54, p<0.001) and total emergency visits by 76% (0.098 vs 0.412, p<0.001) compared with placebo in the 28-week treatment period.[70] These data compare with 26%, 50% and 44% reductions, respectively, in the overall omalizumab-treated population.[49] In addition, the percentage of patients with a clinically meaningful improvement in QoL was 79% in omalizumab-treated responders compared with 35% of non-responders.[70] The physician's overall assessment as a tool for evaluating response to omalizumab has not yet been prospectively studied in a naturalistic clinical practice setting, and it remains to be seen if future studies conducted in this setting confirm the results from these post-hoc analyses of clinical trial data.

Cost-effectiveness

Identifying responders in clinical practice is of great importance. Not all patients respond equally to omalizumab, and in the EU label, physicians should assess the patient's response to omalizumab at 16 weeks before deciding to continue long-term treatment. Treatment should only be continued if the physician judges that the patient has

Table 4. Annualised clinically significant exacerbation rates by various responder definitions (INNOVATE).[70]

		Clinically signifcant exacerbations			
	% responders	Responder		Non-responder	
Response measure		n	Rate (SD)	n	Rate (SD)
Physician's overall assessment complete control or marked improvement	61	118	0.6 (1.31)	77	2.6 (6.39)
AQLQ ≥0.5 improvement	61	124	0.8 (1.45)	80	1.7 (2.90)
FEV_1 ≥200 mL improvement	44	90	1.2 (2.39)	116	1.1 (2.00)
Daytime symptom score ≥1.0 reduction	21	36	0.3 (0.83)	140	1.7 (4.96)
Nocturnal symptom score ≥1.0 reduction	18	32	0.4 (0.87)	146	1.6 (4.87)
Night awakenings reduced ≥1/week and by 50%	32	57	0.8 (2.13)	121	1.7 (5.18)

Imputed exacerbations resulted in some patients with high exacerbation rates not being included in all analysis populations. Therefore, to enable meaningful direct comparisons, all exacerbation rates presented are without imputation. Clinically significant exacerbations were defined as a worsening of asthma requiring treatment with systemic corticosteroids.

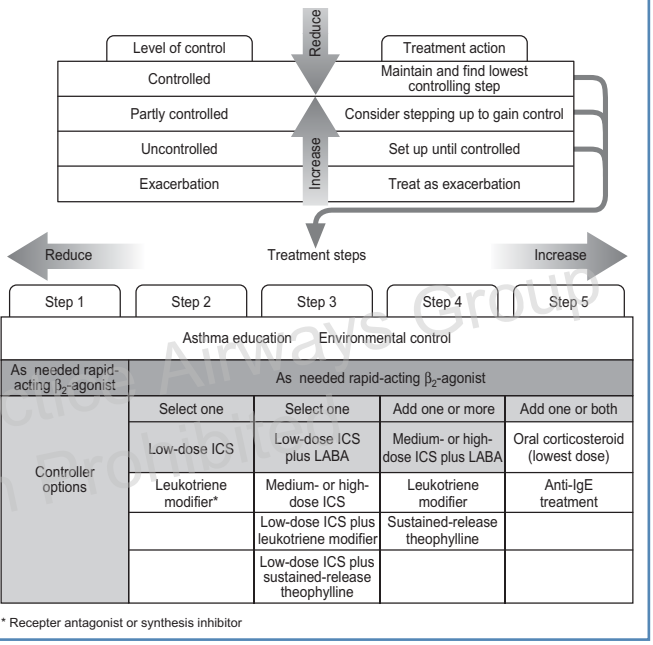
SD = standard deviation; AQLQ = Asthma Quality of Life Questionnaire; FEV_1 = forced expiratory volume in 1 second

Table 5. Annualised exacerbation rates, unscheduled healthcare utilisation and other asthma control measures by physician's overall assessment responders and non-responders to omalizumab (INNOVATE).[70]

	Responder	Non-responder
Clinically significant exacerbations		
Rate, mean (SD)	0.6 (1.31)	2.6 (6.39)
Severe exacerbations		
Rate, mean (SD)	0.2 (0.6)	1.4 (6.1)
Hospitalisations†		
Patients hospitalised in treatment phase, %	2.5	9.1
Rate, mean (SD)	0.03 (0.22)	0.10 (0.35)
Emergency room visits†		
Rate, mean (SD)	0.02 (0.17)	0.17 (0.80)
Unscheduled physician visits†		
Rate, mean (SD)	0.11 (0.44)	0.49 (1.31)
Any unscheduled healthcare utilisation		
Rate, mean (SD)	0.20 (0.61)	1.50 (6.14)
Asthma symptom score, mean (SD)*	–1.24 (1.82)	–0.47 (1.72)
Night awakenings due to asthma, per week mean (SD)*	–1.23 (2.22)	–0.28 (2.74)
Daily rescue medication use, puffs mean (SD)*	–2.32 (3.93)	–0.17 (3.79)
FEV_1 (mL) mean (SD)*	252 (521)	87 (445)
AQLQ improvement ≥0.5-point, % of patients	78.8	34.7

†Rates in the previous year were similar for responders and non-responders. *Values are changes from baseline. SD = standard deviation; FEV_1 = forced expiratory volume in 1 second; AQLQ = Asthma Quality of Life Questionnaire

Figure 6. Adapted from the GINA 2007 report.[7] GINA 2006 guidelines describe a step-wise treatment of asthma. Step 1 involves as-needed reliever medication including short-acting β_2-agonists; step 2, reliever medication plus a single controller medication including low-dose ICS and leukotriene modifiers; step 3, reliever medication plus one or two controller medications, the recommended option being low-dose ICS plus LABA; step 4, reliever medication plus two or more controller medications, the preferred option being medium or high-dose ICS plus LABA; step 5, reliever medication plus additional controller medications including anti-IgE and/or oral corticosteroids. ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist.



achieved a marked improvement or complete asthma control. By selecting only patients that appear to respond to omalizumab at 16 weeks, treatment is targeted to improve overall effectiveness, minimise unwarranted exposure and maximise cost-effectiveness. Indeed, cost-effectiveness analyses of omalizumab that accounted for responder status have shown that omalizumab is cost-effective in patients with severe persistent allergic asthma.[73,74]

One analysis[73] applied data from the INNOVATE[49] study to Sweden as a reference country and calculated an incremental cost-effectiveness ratio (ICER) of €56,091, slightly higher than the Swedish accepted threshold of €53,384 (SEK 500,000). The annual cost of treatment with omalizumab, based on the dose distributions observed in INNOVATE was calculated to be €15,444. This annual cost takes into account the administration costs by a general practitioner (GP), and varies between €536 and €2,352 per month for the lowest and highest dose users. Another analysis[74] applying ETOPA data[50] to Canada calculated an ICER of €31,209, below the Canadian ICER threshold of €35,000 (CAD$50,000). Annual drug costs for omalizumab during the ETOPA study (based on an average 27.7 vials over the 52-week trial) were €11,634. In these studies, the ICER is defined as the difference in total costs between treatments per quality-adjusted life year (QALY), with a lower ICER value indicating greater cost-effectiveness. The authors of the Canadian study argue that their analysis, based on a 1-year open-label study in a naturalistic setting, is more likely to reflect real-life outcomes than the 28-week clinical trial setting of the Swedish study.

Conclusions

Despite receiving high-dose ICS plus LABA, many patients with severe allergic (IgE-mediated) asthma remain symptomatic. Anti-IgE therapy (omalizumab) is now included in the GINA guidelines as add-on therapy to ICS plus LABA and other controller medications (Figure 6). There is evidence from clinical studies, including INNOVATE, of the effectiveness of omalizumab in reducing exacerbations and total

emergency visits and improving QoL in patients meeting the definition of both moderate-to-severe and severe persistent allergic asthma. Importantly, these benefits appear to be greater in patients who were judged by physicians to have responded to omalizumab therapy. As it is not possible to predict reliably which patients will respond to omalizumab, eligible patients should receive a suitable trial (16 weeks in the EU label) of omalizumab therapy and a decision on further treatment should be made by the physician; it appears best to base this decision on the overall assessment of response. Omalizumab should only be continued in patients judged to have achieved a marked improvement in asthma control or complete asthma control.

Acknowledgement

The author was assisted in the preparation of this text by professional medical writers Dr Dominic Hague (contracted) and Thomas McMurray (ACUMED); this support was funded by Novartis Pharma AG. The views and opinions expressed within the text are those of the author. The medical writers worked entirely under the direction of the author, who received no financial support.

Conflict of interest declaration

DP has no shares in pharmaceutical companies. He has received speaker's honoraria for speaking at sponsored meetings from the following companies marketing respiratory products: 3M, Altana, Astra Zeneca, BI, GSK, IVAX, MSD, Novartis, Pfizer, Schering-Plough. He has received honoraria for advisory panels with; 3M, Altana, Astra Zeneca, BI, GSK, IVAX, MSD, Novartis, Pfizer, Schering-Plough. He or his research team have received funding for research projects from: 3M, Altana, Astra Zeneca, BI, GSK, IVAX, MSD, Novartis, Pfizer, Schering-Plough, Viatris.

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Appendix A: Table 1. Summary of omalizumab controlled studies.

Study	Patient population (n)	Patients with severe persistent asthma*, n (%)	Treatment arms†	Duration (weeks)	Main outcomes
INNOVATE[49]	Inadequately controlled severe asthma despite GINA 2002 step 4 therapy (419)	419 (100)	OMA + CAT vs placebo + CAT	28	Clinically significant exacerbation rate/patient: omalizumab 0.68, placebo 0.91, p=0.042 Severe exacerbation rate/patient: OMA 0.24, placebo 0.48, p=0.002
ETOPA[50]	Inadequately controlled moderate-to-severe asthma (312)	294 (94.2)	OMA + CAT vs CAT alone	52	Asthma deterioration incident rate/year: OMA 4.92, control 9.76, p<0.001 Exacerbations/patient/year: OMA 1.12, control 2.86, p<0.001
SOLAR[51]	Comorbid moderate-to-severe asthma and rhinitis (405)	364 (89.9)	OMA + CAT vs placebo + CAT	28	% patients with exacerbations: OMA 21%, placebo 30%, p=0.02 Exacerbations/patient: OMA 0.25, placebo 0.40, p=0.02
Busse[52,53]	Severe asthma (525)	523 (99.6)	OMA + CAT vs placebo + CAT	52[a]	Exacerbations/patient in stable-steroid phase (16 weeks): OMA 0.28, placebo 0.54, p=0.006 Exacerbations/patient in steroid-reduction phase (12 weeks): OMA 0.39, placebo 0.66, p=0.003 Exacerbations/patient in extension phase (24 weeks): OMA 0.60, placebo 0.83, p=0.023
Solèr[54,55]	Moderate-to-severe asthma (546)	537 (98.4)	OMA + CAT vs placebo + CAT	52[a]	Exacerbations/patient in stable-steroid phase (16 weeks): OMA 0.28, placebo 0.66, p<0.001 Exacerbations/patient in steroid-reduction phase (12 weeks): OMA 0.36, placebo 0.75, p<0.001 Exacerbations/patient in extension phase (24 weeks): OMA 0.48, placebo 1.14, p<0.001
Holgate[56]	Severe asthma dependent on high-dose ICS (341)	315 (92.4)	OMA + CAT vs placebo + CAT	32[b]	Reduction in fluticasone dose: OMA 57%, placebo 43.3%, p=0.003 Exacerbations/patient in stable-steroid phase (16 weeks): OMA 0.15, placebo 0.23, p=NS Exacerbations/patient in steroid-reduction phase (16 weeks): OMA 0.19, placebo 0.34, p=NS
ALTO[57]	Moderate-to-severe asthma (n=1,760)	1,556 (88.4)	OMA + CAT vs CAT alone	24	Exacerbation rate/year/patient: OMA 1.02, control 1.20, p=0.08

OMA = omalizumab; CAT = current asthma therapy; ICS = inhaled corticosteroids

*GINA 2002 classification; †All patients were receiving ICS; long-acting β_2-agonists (LABAs) were not used in studies 4 and 5; [a]28-week core study (16-week steroid-stable phase and 12-week steroid-reduction phase) and 24-week extension; [b]16-week steroid-phase and 16-week steroid-reduction phase.