



REVIEW

Management of asthma with anti-immunoglobulin E: A review of clinical trials of omalizumab

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Summary Immunoglobulin E (IgE) is a key mediator of the inflammatory reactions that are central to the pathogenesis of allergic diseases such as asthma and rhinitis. The recognition of the importance of IgE in allergic disease led to the development of omalizumab, a humanized monoclonal anti-IgE antibody that binds free circulating IgE and prevents the interaction between IgE and high-affinity (Fc ϵ RI) and low-affinity (Fc ϵ RII) IgE receptors on inflammatory cells. By removing free IgE, omalizumab also markedly downregulates the expression of high-affinity receptors on basophils, mast cells and dendritic cells. Several studies have shown that omalizumab effectively reduces the risk of exacerbations and hospitalization and improves symptom control, lung function and quality of life in patients with severe persistent allergic asthma. Importantly, omalizumab has been shown to be effective in patients with poorly controlled severe persistent allergic asthma, a group of patients with few effective additional treatment options. In addition, omalizumab has been shown to provide effective relief from the symptoms of allergic rhinitis (including patients with concomitant asthma). Patients with uncontrolled severe persistent allergic asthma are a challenging and difficult-to-treat population for whom omalizumab might represent an important new treatment option. In addition, omalizumab may provide a means to address comorbid allergic disease in patients with asthma. Further investigation is also warranted to explore potential applications of omalizumab in occupational asthma.

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Introduction

Immunoglobulin E (IgE) has been known to be a key mediator of allergic reactions for more than 30 years and plays a central role in allergic responses to allergens in patients with asthma and rhinitis.^{1,2} IgE is produced by B cells after sensitization to an allergen³ and has a short half-life.⁴ Despite low serum concentrations, IgE is immunologically highly active due to the large number of high-affinity IgE receptors on mast cells and basophils.³ In addition, IgE up-regulates receptors on several cell types, including basophils and mast cells.^{4,5} The binding of IgE to the receptors on these cells results in the formation of cross links between the allergen and the IgE molecule and initiates the inflammatory cascade through release of a variety of mediators, including histamine, leukotrienes (LT), and platelet-activating factor.⁶

Current evidence suggests that the majority of asthma has an allergic basis^{7,8} and that IgE is central to the initiation of both allergic and non-allergic asthma.^{9–11} Indeed, population studies indicate that almost all asthma is associated with elevated IgE levels.¹² In addition, IgE also plays a central role in many cases of occupational asthma¹³ as well as in a variety of allergic conditions, including rhinitis.¹⁴

The central role of IgE in allergic disease created interest in developing treatments based on anti-IgE antibodies. In particular, it was hoped that new treatments based on anti-IgE approaches might

provide a means to improve control of allergic asthma and better meet the goals set out in the Global Initiative for Asthma (GINA) guidelines.¹⁵ According to the GINA guidelines, treatment should be adjusted using a stepwise approach based on asthma severity. Treatment for mild intermittent asthma (step 1) is based on use of rescue bronchodilators as needed, with increasing doses of inhaled corticosteroids (ICS) used to control mild (step 2), moderate (step 3), and severe (step 4) persistent asthma. Patients with moderate persistent asthma should also receive a long-acting β_2 -agonists (LABA) or alternatively sustained-release theophylline, an oral β_2 -agonists or a LT modifier. For patients with severe persistent asthma, high-dose ICS and LABA are recommended with additional agents added if required. The Gaining Optimal Asthma Control (GOAL) study showed that many patients fail to achieve control of asthma despite treatment with corticosteroids (fluticasone) or combination salmeterol/fluticasone therapy.¹⁶ Although the GOAL study showed that using combined salmeterol and fluticasone increased the percentage of patients achieving control of their asthma, many patients remained inadequately controlled, especially in the group with the most severe asthma where 38% and 53% of patients remained inadequately controlled despite treatment with salmeterol/fluticasone and fluticasone, respectively (Table 1).

The association between an increased risk of death and factors characteristic of more severe

Table 1 Percentage of patients who were not totally controlled or well controlled in the GOAL study.¹⁶

Stratum	Patients not totally controlled or well controlled (%)	
	Fluticasone/salmeterol	Fluticasone
1. Corticosteroid naïve	22	30
2. ≤ 500 $\mu\text{g/day}$ BDP or equivalent	25	40
3. > 500 to ≤ 1000 $\mu\text{g/day}$ BDP	38	53

BDP = beclometasone dipropionate.

disease has been evident for many years. For example, Rea et al.¹⁷ found that previous hospital admission for asthma increases the risk of death 16-fold. More recent studies indicate that a history of severe asthma is associated with a greater than 6-fold increase in the risk of death within 3 years of discharge from hospital.¹⁸ The high risk of morbidity and mortality means that achieving the best possible control of severe asthma should be a high priority. Unfortunately, as noted in the GINA guidelines, complete control of severe asthma is often not possible with currently available treatments¹⁵ and, therefore, an urgent need exists for improved options to manage severe persistent asthma, especially in patients with inadequate control using currently available treatment regimens.

The role of IgE in allergic diseases other than asthma also raises the possibility that anti-IgE approaches could have broader applications than conventional asthma medications. In particular, strong evidence shows that allergic asthma and rhinitis represent different facets of a common inflammatory process affecting both the upper and lower respiratory tract,³ but that the central role of IgE in both conditions means that effective treatments targeting inflammation mediated by IgE might be clinically useful in both conditions, especially in light of the high prevalence of comorbid asthma and rhinitis. Findings from epidemiological studies suggest that between 60% and 80% of patients with asthma have rhinitis, while 20–40% of patients with rhinitis have asthma.^{19–21} In addition, a variety of substances can trigger occupational asthma and there is evidence of elevated IgE levels in large numbers of people exposed to numerous agents found in the workplace.^{22–25} There may therefore be potential applications of anti-IgE therapies, such as omalizumab, in the management of occupational asthma associated with elevated IgE.

Omalizumab, currently the only anti-IgE agent available for the treatment of allergic asthma, has been investigated in several clinical studies of allergic rhinitis. This article therefore evaluates the evidence from clinical trials of omalizumab, with a focus on the treatment of severe persistent asthma, and discusses potential applications in clinical practice.

Mechanism of action of omalizumab

Omalizumab is a humanized monoclonal anti-IgE antibody that binds to the high-affinity and low-

affinity receptor regions of the IgE molecule (Cε3 domain) thereby preventing free IgE from interacting with IgE receptors.²⁶ By binding to the allergen-specific region of the IgE molecule, but not cell-bound IgE, omalizumab inhibits allergen-induced responses without causing receptor cross-linking, which could lead to anaphylaxis.

Reductions in free IgE alone would not likely be sufficient to block IgE-mediated inflammatory reactions because the high density of receptors on effector cells require at least a 99% reduction in levels in the circulation.²⁷ However, as well as reducing circulating IgE levels by approximately 99%, omalizumab down-regulates receptor expression on basophils.^{28–30} A study of the reversibility of this down-regulation of receptor expression suggested that it was a consequence of the reductions in serum IgE caused by omalizumab.³⁰ It therefore appears that omalizumab acts by directly reducing free IgE levels, which in turn leads to reduced receptor expression on effector cells. Recent studies have also reported that omalizumab down-regulates high-affinity IgE receptor (FcεRI) expression on dendritic cells.^{31–33}

The combined effect of reduced free IgE levels and down-regulation of receptor expression could theoretically result in potent inhibition of IgE-mediated inflammatory reactions. Consistent with this hypothesis, omalizumab reduces both the early and the late asthmatic responses,^{34,35} with significant improvements in forced expiratory volume in 1 s (FEV₁) after allergen challenge during both phases (Fig. 1),³⁵ as well as reducing the number of IgE+ and FcεRI+ cells in the bronchial submucosal and epithelial tissues of patients with asthma.³⁶ Omalizumab reduces numbers of IgE-positive cells and local and systemic IgE production in patients with allergic rhinitis^{37,38} as well as eosinophilia in patients with allergic asthma.³⁶ Given recent evidence that the prevalence of high-affinity IgE receptor expression is approximately 3-fold higher in cases of fatal asthma than in mild intermittent asthma,³⁹ reducing numbers of IgE+ and FcεRI+ cells³⁶ may be particularly important in reducing mortality due to asthma. The effects of omalizumab on eosinophil numbers may also be important in light of the relationship between eosinophilia, airway inflammation, asthma severity, and the risk of exacerbations.^{40,41} In addition, as FcεRI receptor expression on dendritic cells is increased in patients with allergic asthma,⁴² the inhibitory effect of omalizumab on dendritic cell FcεRI expression suggests that omalizumab may alter allergen presentation, a fundamental step in the allergic response.

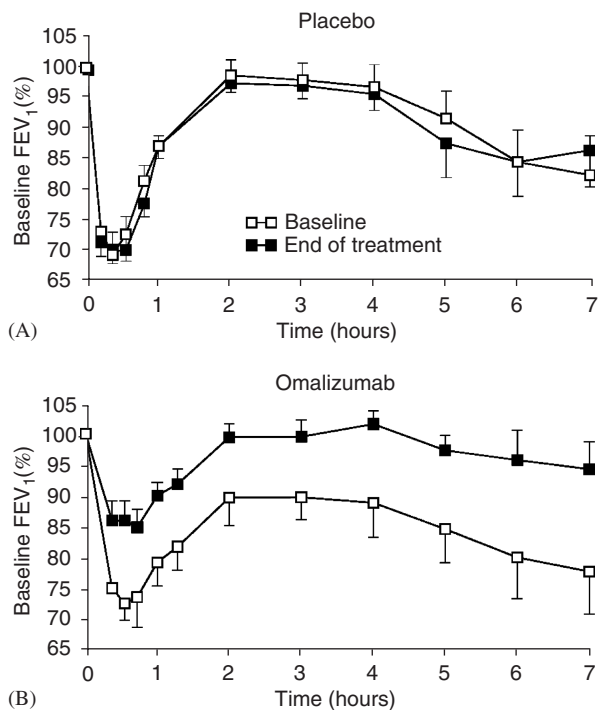


Figure 1 Forced expiratory volume in 1 s (FEV₁) as a percentage of baseline in the first hour after allergen challenge (early phase response) and from 2 to 7 h after allergen challenge (late phase response) in the placebo group (A) ($n = 9$) and omalizumab group (B) ($n = 9$) at baseline (open squares) and at the end of treatment (closed squares). Reproduced with permission.³⁵

Omalizumab in allergic asthma

Patients who fail to achieve adequate control of severe persistent asthma despite receiving LABAs and ICS in line with the GINA guidelines are at a high risk of morbidity and mortality and have limited treatment options. The high risk of morbidity and mortality in severe asthma, combined with the limited treatment options available for patients with inadequately controlled severe asthma, provided a strong rationale for investigating the efficacy of omalizumab in this patient population. The INvestigationN of Omalizumab in seVere Asthma TrEatment (INNOVATE) study exclusively enrolled patients with inadequately controlled severe persistent allergic asthma despite GINA 2002 step 4 therapy.⁴³ In addition, the efficacy of omalizumab was also investigated in 3 other double-blind, placebo-controlled studies^{44–48} and an open-label study in patients with allergic asthma⁴⁹ as well as a study of patients with concomitant asthma and persistent allergic rhinitis.⁵⁰ Although these studies were initiated prior to GINA 2002 guidelines, subsequent analysis found that >90% of patients

in each study met GINA 2002 criteria for severe persistent asthma.⁵¹

Clinical efficacy

INNOVATE was a double-blind, multicentre, parallel-group study in which patients were randomized to receive omalizumab ($n = 209$) or placebo ($n = 210$) for 28 weeks.⁴³ At the end of this 28-week period, patients receiving omalizumab had a 26% reduction in the rate of clinically significant asthma exacerbations (defined as a worsening of asthma symptoms requiring treatment with systemic corticosteroids and adjusted for baseline exacerbation history) compared with placebo (0.68 versus 0.91, $P = 0.042$) (Table 2; Fig. 2). Without adjustment, a similar magnitude of effect was seen (19% reduction), but this did not attain statistical significance (0.74 versus 0.92, $P = 0.153$). Consistent with this finding, omalizumab also reduced severe exacerbations (defined as peak expiratory flow [PEF] or FEV₁ <60% of personal best, requiring systemic corticosteroids) by 50% (0.24 versus 0.48, $P = 0.002$) (Fig. 2) and emergency visits by 44% (0.24 versus 0.43, $P = 0.038$). The reduction in asthma exacerbations and hospital admissions in patients receiving omalizumab was also reflected in significantly greater improvements in morning PEF ($P = 0.042$), FEV₁ percent predicted values ($P = 0.043$), and total asthma symptom scores ($P = 0.039$) compared with placebo recipients. The effectiveness of omalizumab was rated as excellent or good by 60.5% of investigators and 64.3% of patients in the INNOVATE study.

The findings of the INNOVATE study were consistent with the results of an open-label study.⁴⁹ During the 52 weeks of this study, patients receiving omalizumab ($n = 206$) in addition to best standard care had approximately half as many asthma-related deterioration incidents as patients receiving best standard care alone ($n = 106$) (4.92 versus 9.76 per patient year, respectively) (Table 2). Treatment with omalizumab also led to a significant reduction in the number of clinically significant asthma exacerbations (1.12 versus 2.86 per patient year, respectively) and a significant increase in the percentage of patients requiring rescue medication less often than once a week (41.4% versus 20.7%, respectively). A recent subgroup analysis of patients with severe persistent asthma enrolled in this open-label study showed that the addition of omalizumab to best standard care resulted in a 59% reduction in the annual rate of asthma exacerbations, compared with best

Table 2 Studies of omalizumab in patients with asthma.

Study	Population	Patients (n)	Treatment groups	Treatment duration	Outcome
Humbert ⁴³ (INNOVATE)	Severe allergic asthma	419	Omalizumab Placebo	28 weeks	Clinically significant exacerbation rate/patient: omalizumab 0.68, placebo 0.91, $P = 0.042$ Severe exacerbation rate/patient: omalizumab 0.24, placebo 0.48, $P = 0.002$
Ayres ⁴⁹	Moderate-to-severe allergic asthma	312	Omalizumab plus BSC BSC	52 weeks	Asthma deterioration incident rate/year: omalizumab 4.92, placebo 9.76, $P < 0.001$ Exacerbations/patient/year: omalizumab 1.12, placebo 2.86, $P < 0.001$ Patients with exacerbations: omalizumab 21%, placebo 30%, $P = 0.02$
Vignola ⁵⁰	Moderate-to-severe asthma and persistent allergic rhinitis	405	Omalizumab	28 weeks	
Busse ⁴⁵	Severe allergic asthma	525	Placebo Omalizumab	28 weeks	Exacerbations/patient: omalizumab 0.28, placebo 0.54, $P = 0.006$
Lanier ⁴⁷ (extension to Busse study)	Severe allergic asthma	460	Placebo Omalizumab	24-week extension	Exacerbations/patient: omalizumab 0.60, placebo 0.83, $P = 0.023$
Solèr ⁴⁸	Moderate-to-severe allergic asthma	546	Placebo Omalizumab	30 weeks	Exacerbations/patient in stable steroid phase (16 weeks): omalizumab 0.28, placebo 0.66, $P < 0.001$ Exacerbations/patient in steroid reduction phase (12 weeks): omalizumab 0.36, placebo 0.75, $P < 0.001$
Buhl ⁴⁴ (extension to Solèr study)	Moderate-to-severe allergic asthma	483	Omalizumab Placebo	24-week extension	Exacerbations/patient: omalizumab 0.48, placebo 1.14, $P < 0.001$
Holgate ⁴⁶	Severe allergic asthma	246	Placebo Omalizumab	32 weeks	Reduction in fluticasone dose: omalizumab 57%, placebo 43.3%, $P = 0.003$ Exacerbations/patient: omalizumab 0.48, placebo 1.14, $P < 0.001$

BSC = best standard care.

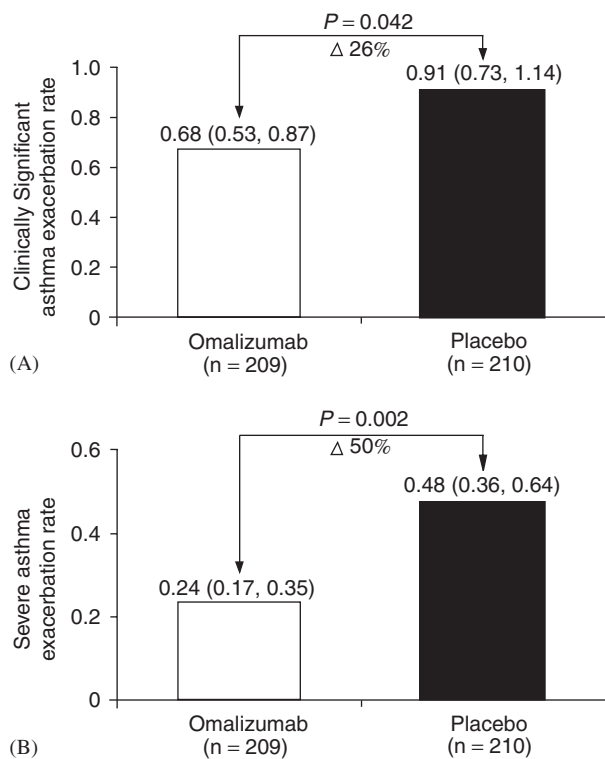


Figure 2 Effect of omalizumab treatment on the rate of (A) clinically significant asthma exacerbations (adjusted for baseline exacerbation history) and (B) severe exacerbations during the 28-week treatment period in the primary intent-to-treat population. Values are means and 95% confidence intervals. Reproduced with permission.⁴³

standard care alone (1.24 versus 3.00, respectively, $P < 0.001$).⁵²

Several other studies have provided additional evidence of the efficacy of omalizumab in patients with severe persistent allergic asthma. Reductions in the incidence of exacerbations in patients receiving omalizumab were reported in 3 randomized, placebo-controlled studies^{45,46,48} (Table 2). The reductions in exacerbations were also accompanied by significant reductions in hospitalization and a significantly greater reduction in the ICS requirements in patients receiving omalizumab compared with those taking placebo (Fig. 3). In a meta-analysis of data obtained in the three studies,^{45,46,48} omalizumab was particularly effective in patients who were at high risk of serious asthma-related morbidity and mortality.⁵³ In another analysis of data from 2 of the 3 studies^{45,48} factors indicative of more severe asthma (history of emergency treatment and high-dose ICS) were predictive of a response to omalizumab.⁵⁴ In addition, 2 of the studies included 24-week extension periods beyond the original 28–30-week studies and demonstrated that the benefits were sustained^{44,47} (Table 2). Omalizumab was highly

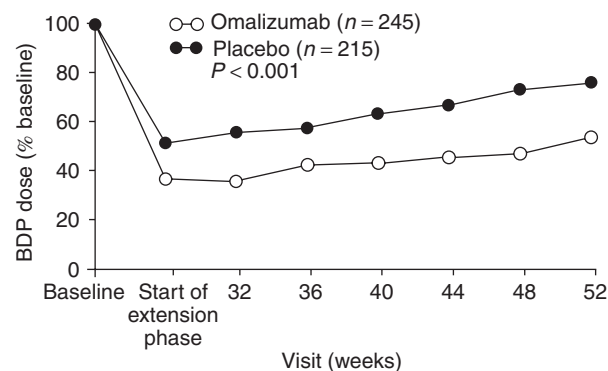


Figure 3 Mean equivalent dose of inhaled beclometasone dipropionate (BDP), expressed as a percentage of baseline in patients with severe asthma (Busse/Lanier study). Reproduced with permission.⁴⁷

rated in subjective evaluations of effectiveness, with 60–70% of patients and investigators describing treatment with omalizumab as excellent or good, compared with approximately 40% for placebo.^{45,55}

In a pooled analysis of the studies of omalizumab, which included the studies described above, Bousquet et al. found that omalizumab significantly reduced the annualized asthma exacerbation rate by 38% ($P < 0.0001$) and the emergency visit rate by 47% ($P < 0.0001$) (Table 3), compared with the control group.⁵¹ It is notable that 93% of patients included in this pooled analysis met GINA 2002 criteria for severe persistent asthma.

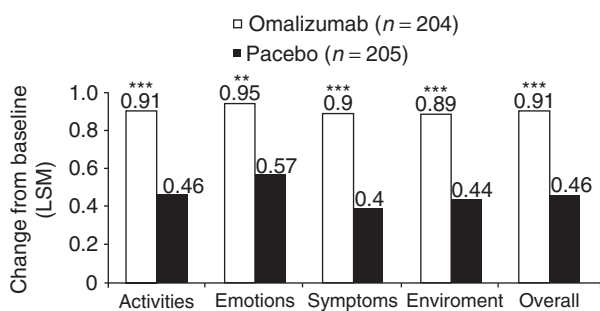
Quality of life

Reducing the incidence of exacerbations and improving symptom control and lung function would be expected to improve quality of life (QoL) for patients with severe persistent asthma. The studies of omalizumab utilized asthma-specific QoL questionnaires (AQLQ).^{56,57} These questionnaires are designed to reflect the areas that patients consider most important: symptoms classically associated with asthma; responses to environmental stimuli; limitation of activities; and emotional dysfunction.

In the INNOVATE trial, more patients receiving omalizumab reported a clinically meaningful improvement of at least 0.5 points on the Juniper AQLQ than patients receiving placebo (60.8% versus 47.8%, respectively).⁴³ The improvements in QoL seen in the INNOVATE study occurred across all 4 domains of the AQLQ (activity limitation, emotions, symptoms, exposure to environmental stimuli) (Fig. 4). A more detailed QoL analysis from another study of omalizumab provided further evidence of

Table 3 Emergency visits in a pooled analysis of clinical trials of omalizumab in patients with predominately severe persistent asthma. Reproduced with permission.⁵¹

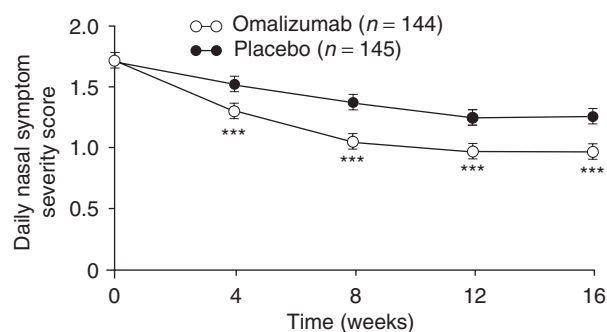
	Rate per year		Treatment difference	Ratio (95% CI)	P-value
	Omalizumab	Control			
Total emergency visits	0.332	0.623	0.291	0.533 (0.401, 0.709)	<0.0001
Hospital admissions	0.030	0.062	0.032	0.489 (0.246, 0.972)	0.041
Emergency room visits	0.026	0.066	0.040	0.397 (0.192, 0.820)	0.013
Unscheduled doctor visits	0.252	0.443	0.191	0.568 (0.417, 0.774)	0.0003

**Figure 4** Change from baseline in AQLQ scores in the INNOVATE study. ** $P < 0.01$ and *** $P < 0.001$ versus placebo.⁴³ LSM = least-squares mean.

the beneficial effects of omalizumab on QoL.⁵⁵ At weeks 28 and 52, patients receiving omalizumab had higher AQLQ scores for all 4 domains and for the total AQLQ score. Similarly, an analysis of QoL from another study showed that omalizumab was associated with significant improvements in all 4 domains of the AQLQ.⁵⁸ A pooled analysis of the QoL outcomes in these 2 studies confirmed that omalizumab resulted in significantly greater improvements in AQLQ in all 4 domains and for the total score, at the end of both the steroid-stable and steroid-reduction phases of the trials. In a recent analysis of QoL from 6 clinical trials, change from baseline in AQLQ score was significantly greater for omalizumab compared with control in all studies.⁵⁹

Omalizumab in allergic rhinitis

Several studies investigated the efficacy of omalizumab in patients with seasonal or perennial allergic rhinitis. In 2 studies of patients with seasonal allergic rhinitis, treatment with omalizumab resulted in significant reductions in daily nasal symptom severity scores.^{60,61} These improvements in nasal symptom scores were associated with

**Figure 5** Mean (\pm standard error) daily nasal severity score for each 4-week period during 16 weeks' treatment with either omalizumab or placebo in adults and adolescents with symptomatic perennial allergic rhinitis. P values for between-treatment comparisons are from an analysis of covariance, adjusting for treatment group, centre, dosing schedule, and baseline value. Reproduced with permission.⁶²

reduced IgE levels and led to decreases in rescue antihistamine use and improved QoL scores. Similar reductions in nasal symptom scores have been reported in patients with perennial allergic rhinitis (Fig. 5).⁶²

This evidence of efficacy in allergic rhinitis, combined with the evidence of effective asthma control described above, indicates that omalizumab would be expected to provide a means to control both conditions in patients with comorbidity. Confirmation of the efficacy of omalizumab for the treatment of comorbid allergic respiratory disease was provided by a study of patients with concomitant allergic asthma and rhinitis.⁵⁰ In this study, patients receiving omalizumab had fewer asthma exacerbations than placebo recipients (Table 2) in addition to lower asthma and rhinitis scores on the Wasserfallen scale.

In a study of 221 children with seasonal allergic rhinitis to both birch and grass pollen, omalizumab provided additional symptomatic benefit when given concomitantly with specific immunotherapy (SIT) to birch or pollen, compared with placebo plus

SIT to either allergen.⁶³ In a subgroup of 92 children from this study, who were receiving omalizumab or placebo plus SIT to grass or birch pollen, ex vivo allergen stimulation of circulating leukocytes showed a decrease in LT release (LTC₄, LTD₄, LTE₄), independent of type of allergen SIT used, in children receiving omalizumab ($P = 0.001$ versus SIT alone).⁶⁴ Thus, children receiving omalizumab plus birch SIT had reduced leukocyte mediator release when stimulated with grass (and birch) allergen, and vice versa. In this study, SIT alone had no effect on LT release.

Omalizumab in occupational asthma

According to the GINA guidelines, allergens and occupational sensitizers are the most important causes of asthma and can cause the initial sensitization of the airways that leads to development of asthma, as well as precipitating subsequent exacerbations and ongoing symptoms.¹⁵ Several studies have indicated that asthma can be caused by occupational exposure to a huge variety of allergens or chemicals, including cow, horse, and laboratory animal dander, flour, mites, platinum salts, biological enzymes and organic chemicals.^{13,65–67}

IgE levels are elevated in many people exposed to known causes of occupational asthma. For example, a population-based survey in Italy showed that people who reported occupational exposure to dusts, chemicals, or gases had significantly higher serum IgE levels than those reporting no exposure (43 versus 35 kU/l, respectively, $P = 0.008$).²⁵ Similar increases in IgE levels have been reported in people exposed to a variety of occupational sensitizers, including dusts and gases,²⁴ rose oil,²² and enzymes used in the detergent industry.²³

At present, there is little direct evidence of the efficacy of omalizumab in other asthmatic populations, such as those with occupational asthma. However, the importance of IgE in the pathophysiology of occupational asthma, combined with evidence of efficacy in latex allergy,⁶⁸ indicates that omalizumab warrants further investigation as a potential treatment for occupational asthma. This is particularly relevant for patients who are unable to avoid allergen exposure in their place of work.

Omalizumab in other allergic conditions

Several studies have shown that omalizumab is effective in a variety of conditions associated with

elevated IgE levels and exposure to a variety of substances, including latex, and peanuts. In health-care workers with latex allergies, treatment with omalizumab was associated with reductions in conjunctival allergen challenge scores at 8 and 16 weeks.⁶⁸ Others have reported that omalizumab may be effective in treating IgE-mediated severe eye allergies.⁶⁹ In addition, patients with peanut allergy who received another anti-IgE antibody, TNX-901, had large increases in the threshold of sensitivity to oral challenge with peanut (from 178 to 2805 mg).⁷⁰ This would be equivalent to an increase in the threshold from approximately half a peanut to almost 9 peanuts, and suggests that anti-IgE agents might be expected to provide useful protection from accidental peanut ingestion.

The efficacy of anti-IgE in a variety of conditions related to IgE and sensitizers such as pollen, latex, and peanuts, indicates that treatment might be beneficial in patients with allergic conditions caused or exacerbated by similar sensitizers. Further clinical trials are needed to explore this potentially useful clinical application of omalizumab.

Safety and tolerability

The safety and tolerability of omalizumab has been extensively evaluated in more than 7500 adult patients with asthma, allergic rhinitis, and related conditions.⁷¹ The nature and frequency of adverse events (AEs) followed a similar pattern in the active and control treatment groups. The most frequent AEs (regardless of relationship to treatment) occurred with similar frequencies in the omalizumab and placebo groups, and included nasopharyngitis (14.4% versus 15.9%, respectively), upper respiratory tract infection (15.7% in both groups), headache (15.5% versus 15.6%, respectively) and sinusitis (10.1% versus 12.0%, respectively). Serious AEs were infrequent in both the omalizumab (4.2%) and control groups (3.8%).

There was no evidence of increased risk of immune-complex mediated or other hypersensitivity reactions, infections or bleeding-related AEs in omalizumab-treated patients. None of the omalizumab-treated patients developed measurable anti-omalizumab antibodies. Clinical evidence does not suggest that omalizumab treatment is associated with an increased risk of malignancy.⁷²

Clinical applications of omalizumab

Inadequate control of asthma places a substantial burden on patients and healthcare providers and

causes high levels of morbidity and mortality. The GINA guidelines specify that patients with severe asthma should receive ICS at doses of at least 1000 $\mu\text{g}/\text{day}$ in combination with LABAs.¹⁵ If these agents fail to achieve control of asthma, the guidelines recommend using additional agents, such as theophylline, LT modifiers, oral β_2 -agonists, or oral corticosteroids. However, the guidelines note that despite treatment, it may not be possible to achieve complete control of severe persistent asthma. At present there is little that can be done to improve asthma control in patients who fail to achieve control despite GINA step 4 therapy. The proven efficacy of omalizumab in patients with inadequately controlled severe persistent asthma⁴³ and the limitations of current options provide a clear rationale for the use of omalizumab as an add-on therapy in this patient population.

There is also a strong rationale for considering the use of omalizumab in the broader population of patients with severe persistent asthma, given the strong evidence of reductions in the incidence of exacerbations, improved asthma symptom scores and pulmonary function tests, and reduced rescue medication use seen in clinical trials.^{45,48,50} The large reductions in annualized asthma exacerbation rate and emergency visits in a combined analysis of the clinical trials of omalizumab suggest that treatment of severe persistent asthma with omalizumab will result in significant reductions in morbidity in this population of patients.⁵¹

The evidence of efficacy in other allergic conditions, especially allergic rhinitis, suggests that omalizumab may also have the potential to address comorbid allergic disease in patients with asthma. The central role of IgE in both allergic asthma and rhinitis, combined with evidence of efficacy in both conditions and in a study of comorbid patients,⁵⁰ indicates that omalizumab might be useful in the management of allergic disease throughout the respiratory tract.

Conclusions

Allergic asthma causes considerable morbidity and mortality and places a large burden on patients and healthcare providers. Despite treatment with LABAs and high daily doses of ICS, many patients have severe persistent asthma that is inadequately controlled and there is little that can be done to improve asthma control in these patients.

The central role of IgE in allergic inflammatory processes presented an attractive target for novel therapies such as omalizumab (Table 4) for patients with allergic disease and particularly for those with severe persistent allergic asthma. Omalizumab is an anti-IgE antibody that significantly reduces serum IgE levels and down-regulates IgE receptor expression in vitro and in vivo. Clinical studies in patients with asthma have provided convincing evidence that omalizumab is effective in patients with severe asthma and that it may be particularly useful in patients whose asthma is inadequately controlled despite GINA step 4 therapy. Indeed, anti-IgE was included as an add-on therapy to high-dose ICS and LABA in the most recent update of the GINA guidelines in 2004.

There is now a large body of evidence demonstrating the central role of IgE in a wide variety of allergic conditions, including diseases of the upper airway (rhinitis) and lower airway (asthma), as well as in occupational asthma. This evidence provides a rationale for considering the potential application of omalizumab to a broader range of allergic disease. Consistent with this rationale, omalizumab has been shown to be effective in patients with allergic rhinitis and in a study of occupational latex allergy. There is therefore strong evidence to support the efficacy of omalizumab in allergic rhinitis and especially in patients with concomitant asthma and rhinitis. Further studies are warranted to explore the benefits of omalizumab in occupational asthma.

Table 4 Summary of the characteristics of omalizumab.

Binds free circulating IgE and prevents the interaction between IgE and high-affinity ($\text{Fc}\epsilon\text{RI}$) and low-affinity ($\text{Fc}\epsilon\text{RII}$) IgE receptors on inflammatory cells, which also results in downregulation of the high-affinity IgE receptors on mast cells, basophils and dendritic cells

Reduces eosinophilia in the airways of patients with allergic asthma

Reduces exacerbation rates and emergency visit/hospitalization rates in patients with severe persistent allergic asthma

Improves quality of life in patients with severe persistent allergic asthma

Improves symptoms in patients with allergic rhinitis (seasonal and perennial) and in patients with concomitant allergic asthma and allergic rhinitis

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