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REVIEW

Omalizumab in the management of patients with allergic (IgE-mediated) asthma

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Abstract: Immunoglobulin E (IgE) is central to the pathophysiology of allergic asthma. Omalizumab, an anti-IgE monoclonal antibody, binds to the FcεRI binding site on free IgE. As a result, circulating free IgE is reduced, IgE is prevented from attaching to mast cells and basophils, and FcεRI receptor expression is down-regulated. The inflammatory response to allergens and the acute and chronic effector phases of allergic inflammation are thereby attenuated. In clinical trials in adults and adolescents, omalizumab reduced asthma exacerbations, severe asthma exacerbations, inhaled corticosteroid requirements, and emergency visits, as well as significantly improving asthma-related quality of life, morning peak expiratory flow and asthma symptom scores in patients with severe allergic (IgE-mediated) asthma. Results from clinical trials in children (<12 years) are consistent with those in the adult population. It is difficult to predict which patients will respond to omalizumab. Responders to omalizumab should be identified after a 16-week trial of therapy using the physician's overall assessment. When treatment is targeted to these responders, omalizumab provides a cost-effective therapy for inadequately controlled severe allergic (IgE-mediated) asthma. Long-term therapy with omalizumab shows the potential for disease-modification in asthma. Ongoing studies are also evaluating the use of omalizumab in other non-asthma IgE-mediated conditions.

Keywords: omalizumab, IgE, allergic asthma

Introduction

Atopy, a genetic predisposition to the production of immunoglobulin E (IgE), is the underlying cause of most cases of asthma.[1–3] In atopic asthma, sensitization to an allergen results from activation of Th2- and B-lymphocytes, leading to release of cytokines such as IL-4 and IL-13 and production of IgE antibodies.[4] IgE antibodies bind to high-affinity (FcεRI) receptors on mast cells and basophils. Subsequent allergen exposure results in the formation of cross-links between cell-bound IgE, leading to cell degranulation and release of pro-inflammatory mediators such as histamine, tryptase, leukotrienes and prostaglandins.[5] These mediators are responsible for early-phase allergic reactions and promote late-phase reactions by stimulating release of IL-4 from mast cells, leading to positive feedback to Th2 lymphocytes and sustained secretion of cytokines. Mast cells also release mediators that promote up-regulation of adhesion molecules in endothelial cells, resulting in accumulation of eosinophils, basophils and lymphocytes, ultimately leading to airway hyperresponsiveness.[5–7]

The pathophysiology of asthma shares a number of similarities with other allergic conditions, especially allergic rhinitis,[8] in which IgE also plays a central role in the

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underlying inflammation. This link between atopy and asthma/rhinitis provides a strong rationale for developing treatments that target IgE.

A previous review provided an overview of the development, mechanism of action and clinical efficacy and safety of the monoclonal anti-IgE antibody, omalizumab.[9] Since its publication, additional studies have been completed and further clinical experience has been gained with the use of omalizumab. The present article therefore provides an update on the treatment of allergic (IgE-mediated) asthma through targeting of IgE with omalizumab, and provide an overview of the current understanding of the anti-inflammatory effects of omalizumab and its potential role in IgE-mediated diseases.

Development of omalizumab

Omalizumab was originally identified using somatic cell hybridization techniques.[10] A murine monoclonal anti-human IgE antibody (MaE11) was found to have activity directed at the FcεRI binding site on the human IgE molecule.[11,12] By grafting the complementarity-determining region of MaE11 on to a human immunoglobulin G (IgG) framework,[13] a humanized omalizumab molecule containing only 5% murine residues was produced. As omalizumab binds to the same binding site as FcεRI, it can neither bind to IgE that is already bound to the surface of a cell[12,13] nor form cross-links between IgE molecules on the cell surface.[14] This inability to cross-link cell-bound IgE, combined with the small amount of murine residue, results in a low risk of anaphylaxis with omalizumab.

IgE, FcεRI and the allergic response

Administration of omalizumab at a dose approximately equal to 0.016 mg/kg IgE (IU/mL) per 4 weeks reduces serum free IgE by between 89% and 99% in patients with allergic asthma,[15,16] and similar reductions have been observed in patients with allergic rhinitis.[17–20] This reduction in free IgE is accompanied by a reduction in the expression of FcεRI on the cell surface. In one study (n = 15), omalizumab treatment resulted in a 99% decrease in free IgE, and a 96% reduction in the median density of FcεRI on basophils following 3 months of therapy.[21] Similarly, a 6-week study in patients with allergic rhinitis (n = 24) revealed a 73% reduction in basophil FcεRI expression within 14 days of treatment.[20] Omalizumab has also been shown to reduce FcεRI expression on skin mast cells in patients with allergic rhinitis[22] and bronchial mast cells in patients with asthma.[23] Furthermore, omalizumab down-regulated FcεRI expression on precursor dendritic cells over 6 weeks in patients with ragweed-sensitive seasonal allergic rhinitis (SAR; n = 24),[20] with similar effects reported in patients with atopic dermatitis over 16 weeks (n = 20).[24] This down-regulation of receptors on dendritic cells might inhibit antigen processing and presentation to T cells, and could potentially result in blockade of the sensitization phase of the allergic response, as well as the effector phase.

By reducing free IgE and down-regulating FcεRI expression on mast cells and basophils, omalizumab attenuates both the early and late allergic responses. In a study of 19 patients with stable, mild, allergic asthma, omalizumab was shown to attenuate reductions in forced expiratory volume in one second (FEV_1) during both the early (0–1 hour) and late (2–7 hours) phases after allergen challenge.[25] Attenuation of early responses was also evident in a study in patients with stable, mild, allergic asthma (n = 20), which showed that treatment with omalizumab significantly ($p < 0.002$) increased the provocation concentration of allergen causing a 15% decline in FEV_1 (PC_{15}).[26] More recently, a study in 24 patients with mild allergic asthma showed that omalizumab reduced the maximal percentage fall in FEV_1 during both the early (0–3 hours after allergen challenge) and late (3–7 hours) phases after allergen challenge.[27]

The effect of omalizumab on airway hyperresponsiveness to methacholine in patients with mild allergic asthma.[25,26] Significant reductions were reported in one study;[26] however, in a larger study of patients with mild-to-moderate persistent asthma and sputum eosinophilia, hyperresponsiveness to methacholine did not improve following 16 weeks of omalizumab therapy.[23] The effect of omalizumab on eosinophils is established (see 'Anti-inflammatory activity' below), leading the authors of the study to conclude that IgE and eosinophils may not be causally linked to methacholine hyperresponsiveness in mild-to-moderate persistent asthma.[23]

Summary of clinical data

Omalizumab is indicated in the USA as add-on therapy for adults and adolescents (12 years of age and older) with moderate-to-severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids (ICS).[28] In Europe, the indication differs in that patients (12 years of age and above) should have severe persistent allergic asthma, a positive skin test or in vitro reactivity to a perennial aeroallergen, reduced lung function ($FEV_1 < 80\%$), frequent daytime symptoms or night-time awakenings, and multiple documented severe asthma exacerbations despite daily high-dose ICS plus a long-acting β_2-agonist (LABA).[29] The data supporting these indications have been reviewed previously[9] and are summarized below

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along with a more detailed evaluation of newly published studies. In addition, in light of the need for new add-on therapies for children with inadequately controlled asthma, studies conducted in a pediatric setting are also reviewed.

Moderate-to-severe asthma

Efficacy of omalizumab

Omalizumab has been evaluated as an add-on therapy in seven large-scale trials in adults and adolescents with moderate-to-severe allergic asthma. Five of these studies were described in detail in the previous review and are summarized in Table 1.[15,16,30–32]

In all seven studies, omalizumab was administered as add-on therapy every 2 or 4 weeks to provide a dose of at least 0.016 mg/kg per IU/mL of IgE according to patients bodyweight and baseline IgE levels using a dosing table.[33] All studies evaluated the effect of omalizumab on asthma exacerbations, among other endpoints. The definition of an asthma exacerbation varied between studies – asthma exacerbation was defined as: worsening of asthma requiring treatment with systemic corticosteroids in three studies,[30,31,34] worsening of asthma requiring treatment with systemic corticosteroids or a doubling of the baseline inhaled corticosteroid dose in three studies[15,16,32] and, in the seventh study, worsening of asthma requiring unscheduled medical care, an emergency room visit or hospitalization and one or more of doubling of ICS dose, increase in dose of oral corticosteroids (OCS) or initiation of systemic corticosteroids.[35] As noted in the previous review, the clinical trials of omalizumab showed that treatment reduced the rate of asthma exacerbations (Table 1) and led to reductions in inhaled corticosteroid requirements.[9] Since the publication of that review, data have become available from another randomized, controlled trial, the INNOVATE study.[34]

The INNOVATE study enrolled 419 patients with severe persistent asthma that was inadequately controlled despite step 4 treatment as described in the Global Initiative for Asthma (GINA) 2002 guidelines.[34,36] After correction for an imbalance in the history of clinically significant asthma exacerbations (defined as worsening of asthma requiring treatment with systemic corticosteroids), the clinically significant asthma exacerbation rate (the primary endpoint) was significantly ($p = 0.042$) lower at week 28 in patients receiving omalizumab (0.68) than in the placebo group (0.91; Figure 1). Prior to this correction, there was a similar, but statistically non-significant, between-group difference in asthma exacerbations (rate ratio 0.806; $p = 0.153$). Without correction for baseline imbalance, omalizumab also resulted in significantly lower rates of severe asthma exacerbations (defined as an exacerbation in which peak expiratory flow (PEF) or FEV_1 was <60% of personal best, and requiring treatment with systemic corticosteroids; 0.24 vs 0.48, $p = 0.002$) and emergency visits

Table 1 Studies of omalizumab in adults and adolescents with moderate-to-severe allergic asthma[35]

Study	Patients		Study treatments	Study duration (weeks)	Annual exacerbation rate		
	n	Characteristics			Between-group difference	Reduction (%)	P-value
Busse study[15]	525	Severe allergic asthma requiring daily ICS	Omal + ICS vs placebo + ICS	52	0.40	40.3%	<0.001
Solèr study[16]	546	Moderate-to-severe allergic asthma, symptomatic despite ICS	Omal + ICS vs placebo + ICS	52	0.70	57.6%	<0.001
Holgate study[31]	341	Severe allergic asthma	Omal + ICS vs placebo + ICS	32	0.42	26.5%	0.165
INNOVATE study[34]	419	Poorly controlled severe persistent allergic asthma	Omal + ICS vs placebo + ICS	28	0.49	26.6%	0.039
ETOPA study[30]	312	Poorly controlled, moderate-to-severe allergic asthma	Omal + CAT vs placebo + CAT	52	1.49	60.4%	<0.001
SOLAR study[32]	405	Moderate-to-severe asthma and persistent allergic rhinitis	Omal + ICS vs placebo + ICS	28	0.29	37.5%	0.027
ALTO safety study[a]	1899	Severe asthma	Omal + CAT vs placebo + CAT	24	0.18	15.3%	0.077
Pooled analysis[35]	4308	Severe (93% of patients) or moderate asthma	Omal vs control	Annualized	0.56	29.3%	<0.0001

[a]Unpublished study (data on file at Novartis).
Abbreviations: Omal, omalizumab; ICS, inhaled corticosteroids; CAT, current asthma therapy.

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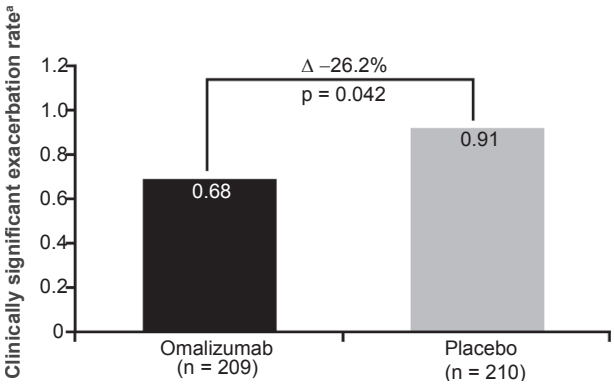

Figure 1 Clinically significant asthma exacerbations in the INNOVATE study. Reproduced with permission from Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy.* 2005;60:309–316. Copyright © 2005 Blackwell Publishing.
[a]Adjusted due to a pre-study imbalance in exacerbation rate.

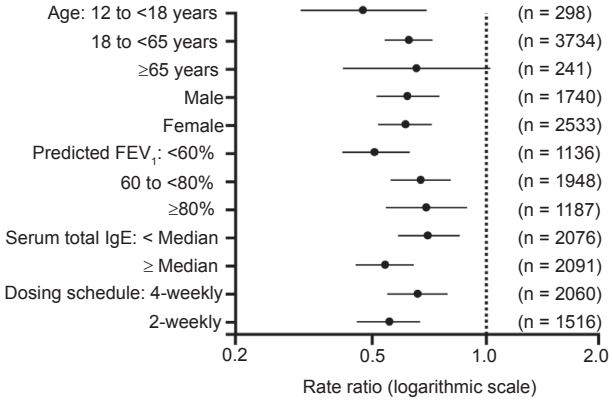

Figure 2 Relative rates of asthma exacerbations across subgroups in pooled studies of omalizumab in patients with moderate-to-severe asthma: point estimates and 95% confidence intervals for asthma exacerbation rate ratios (omalizumab: control) from Poisson regression models. Reproduced, with permission, from Bousquet J, Cabrera P, Berkman N, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy.* 2005;60:302–308.[35] Copyright © 2005 Blackwell Publishing.
Abbreviations: FEV_1, forced expiratory volume in 1 second; IgE, immunoglobin E.

(0.24 vs 0.43, p = 0.038) as well as significant improvements in asthma-related quality of life ($p < 0.001$), morning PEF (p = 0.042) and asthma symptom scores (p = 0.039).

The INNOVATE trial was included in a pooled analysis, along with the six other studies.[35] The pooled population consisted of 4308 patients, 93% of whom had severe persistent asthma according to the GINA 2002 classification. In omalizumab recipients, the rate of asthma exacerbations was reduced by 38% ($p < 0.0001$) and the rate of total emergency visits by 47% ($p < 0.0001$) compared with the control groups. Subgroup analyses showed that age, gender, baseline serum IgE and dosing schedule did not affect the efficacy of omalizumab on asthma exacerbation rates (Figure 2). However, treatment benefits appeared to be numerically greater in patients with lower percentage predicted FEV_1 values.

Reflecting the European label population, an analysis of the severe subpopulation from a 1-year open-label study[30] in patients with moderate-to-severe allergic asthma has recently been published.[37] The analysis found that, in the severe subpopulation, adding omalizumab to best standard care (BSC) significantly improved efficacy outcomes compared with BSC alone. The analysis included 164 patients (omalizumab n = 115; control, n = 49) receiving high-dose ICS plus a LABA. At 1 year, the annual asthma exacerbation rate was reduced by 59% in omalizumab-treated patients, compared with the control group (1.26 vs 3.06; $p < 0.001$), and there were also significant improvements in percentage predicted FEV_1 ($p < 0.05$), asthma symptoms ($p < 0.05$) and mini-Asthma Quality of Life Questionnaire scores ($p < 0.001$).

Data from the seven studies included in the pooled analysis have been analysed to determine whether pre-treatment characteristics could be used to predict outcomes, and to evaluate methods of identifying treatment responders.[38] Analysis of INNOVATE study data showed that baseline total IgE was the only predictor of efficacy; however, pooled data analysis showed that treatment was beneficial regardless of IgE levels. Overall, the analyses showed that it is not possible reliably to predict the outcomes of omalizumab treatment based on pre-treatment characteristics. To identify responders, the physician's overall assessment after 16 weeks of omalizumab therapy provided the best discrimination of treatment outcomes. The physician's overall assessment comprises multiple aspects of response, including patient interview, review of medical notes, spirometry, symptom diaries, rescue medication use and PEF. In omalizumab clinical trials, a physician's overall assessment was graded in a five level evaluation (complete control; marked improvement in control; discernible but limited control; no appreciable change; worsening in control). Patients achieving complete or marked improvement in control were classified as responders. Based on the findings from these analyses, it is recommended that targeting omalizumab to patients most likely to benefit can best be achieved by using the physician's overall assessment to identify responders at 16 weeks, rather than by selecting patients according to baseline characteristics.[38] The ongoing EXHALT study will examine the persistency of treatment response to 32 weeks in patients classified as responders after 16 weeks.[39]

Pediatric asthma

Atopic diseases such as asthma, rhinitis and atopic dermatitis are increasingly prevalent among children.[40] The International

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Study of Asthma and Allergies in Childhood (ISAAC) surveys indicated that severe asthma affects 2.0% to 8.3% of 13- to 14-year-old children and 1.4% to 6.9% of 6- to 7-year-olds in Western Europe, with similar prevalences in the USA (6.1% of 13- to 14-year-olds).[41] Control of asthma in children is also far from optimal. The Asthma Insights and Reality in Europe (AIRE) study showed that only 5.8% of children with asthma met all of the GINA 2002 criteria for asthma control.[42] While lack of asthma control may often be due to inadequate treatment, there is also evidence that many children have poorly controlled asthma despite intensive treatment. For example, a US survey showed that 53% of children (6–11 years) and 44% of adolescents (12–17 years) required an OCS burst and 25% and 19%, respectively, had an emergency room visit in the previous 3 months, despite using three or more long-term controller medications.[43] There is clearly a need to improve asthma control in many children with severe asthma.

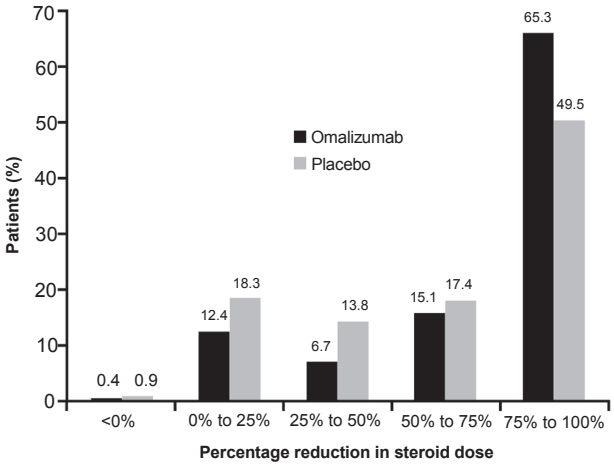

Figure 3 Percentage of patients with reduction in dose of inhaled steroid at end of treatment in a study of omalizumab in a paediatric setting. Reproduced with permission from Milgrom H, Berger W, Nayak A, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics*. 2001;108:E36.[44] Copyright © 2001 by the AAP.

Efficacy of omalizumab

Although omalizumab is not currently indicated in patients <12 years, the efficacy and safety of omalizumab has been evaluated in two double-blind, randomized, placebo-controlled studies. The first enrolled 334 children (aged 6–12 years) with moderate-to-severe allergic (IgE-mediated) asthma that was well controlled with ICS.[44] Children completed a run-in phase during which they were switched to equivalent doses of beclomethasone and the dose adjusted to maintain asthma control, before randomization to add-on omalizumab or placebo. Beclomethasone doses were kept constant during a 16-week stable-steroid phase, reduced during an 8-week steroid-reduction phase, and then kept constant for the remaining 4 weeks of the study. At the end of the study, children in the omalizumab group had achieved significantly greater median reductions in beclomethasone dose than those receiving placebo (primary endpoint; 100% vs 66.7%, $p = 0.001$; Figure 3). In the omalizumab group, 55% of children were able to discontinue ICS, compared with 39% of the placebo group ($p = 0.004$). Despite the reductions in ICS doses, children receiving omalizumab had fewer asthma exacerbations requiring treatment with doubling of beclomethasone dose or systemic corticosteroids, compared with placebo. Additionally, investigators were more likely to rate the effectiveness of omalizumab as excellent (31.5%) or good (44.7%), compared with placebo (16.3% and 32.7%, respectively), with similar results for the patients' ratings of treatment effectiveness. Quality of life, assessed using the Paediatric Asthma Quality of Life Questionnaire (PAQLQ), showed significant ($p < 0.05$) improvements in the activities and symptoms domain scores as well as in overall quality of life at the end of the steroid-reduction phase in the omalizumab group, compared with placebo.[45] Omalizumab recipients were also more likely to have clinically relevant changes in PAQLQ scores (≥0.5 point improvement) during the study, with significant ($p < 0.05$) differences for activities and overall quality of life.

More recently, a 52-week study evaluated the efficacy and safety of omalizumab in 628 children with inadequately controlled, moderate-to-severe persistent allergic (IgE-mediated) asthma.[46] Children received an optimized asthma care programme and were randomized (2:1) to either omalizumab or placebo during a 24-week fixed steroid phase and 28-week adjustable steroid phase. Efficacy was evaluated in 576 children (omalizumab, n = 384; placebo, n = 192), the primary efficacy variable being the rate of clinically significant asthma exacerbations during the fixed-steroid period. The rate of clinically significant asthma exacerbations during the 28-week steroid-adjustable phase was also assessed. After the 24-week fixed-dose steroid treatment period, children treated with omalizumab showed a 31% decrease in the rate of clinically significant asthma exacerbations compared with placebo (0.45 vs 0.64, $p = 0.007$). During the following 28 weeks, children treated with omalizumab showed a 54.2% decrease in the clinically significant asthma exacerbation rate compared with placebo (0.32 vs 0.71, $p < 0.001$). Of note, in the sub-group of children who were receiving high-dose ICS and LABA (corresponding to the current EU indication in adults), children treated with

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omalizumab showed a 34% decrease ($p = 0.047$) in the rate of clinically significant asthma exacerbations compared with placebo during fixed steroid phase, and a 63% decrease ($p < 0.001$) during the adjustable steroid phase.

Allergic rhinitis

Allergic asthma and allergic rhinitis frequently co-exist, and are often considered to be components of a single IgE-mediated inflammatory condition.[47,48] Several trials of omalizumab have been conducted in patients with allergic rhinitis, and have been reviewed previously.[9] In brief, they included two studies in patients with SAR[17,18] and one in patients with perennial allergic rhinitis (PAR).[49] In all three studies, omalizumab significantly reduced symptom severity and rescue antihistamine use, as well as significantly improving rhinitis- or rhinoconjunctivitis-related quality of life in SAR (quality of life was not assessed in PAR). The previous review also summarized the results of the SOLAR study, which evaluated omalizumab in patients with concomitant asthma and PAR,[32] and showed that in addition to reducing asthma exacerbations (Table 1), omalizumab also improved asthma and rhinitis scores on quality of life scales and led to significant ($p < 0.001$) improvements in rhinitis symptoms.

A recent *post hoc* analysis of data from SOLAR showed that the omalizumab-treated patients who achieved the greatest benefits in terms of their asthma symptoms also had the best outcomes for their rhinitis symptoms.[50] In this analysis, patients were classified as asthma responders based on the physician's overall assessment, while rhinitis responders were identified using the Rhinitis Quality of Life Questionnaire (RQLQ) questionnaire. Among the 123 (59.4%) omalizumab-treated patients who were identified as asthma responders, there was a significantly ($p < 0.001$) greater likelihood of a rhinitis response, compared with placebo. Omalizumab-treated asthma responders were also more than 3 times as likely to have a rhinitis response than omalizumab-treated patients who were not classified as asthma responders (odds ratio 3.56; 95% CI 1.94–6.54; $p < 0.05$). As well as providing further evidence of the etiological link between rhinitis and asthma, these results suggest that omalizumab may provide additional benefit to omalizumab-treated asthma patients who also suffer with allergic rhinitis.

Immunotherapy

Allergen-specific immunotherapy (SIT) involves a gradual administration of increasing quantities of a standardized allergen extract to an allergic subject over time in order to alleviate the allergic response of that subject to the causative allergen.[51] The recognition of IgE as a key mediator in allergic disease and the interruption of the allergic cascade with omalizumab have led to the hypothesis that administration of omalizumab with SIT may increase the safety and efficacy of SIT. Accordingly, several studies have evaluated omalizumab in conjunction with SIT. Casale et al investigated the addition of omalizumab to rush immunotherapy (RIT) in adults with ragweed allergic rhinitis.[52] Patients ($n = 159$) received 9 weeks of omalizumab or placebo, followed by 1-day of RIT or placebo immunotherapy and a further 12 weeks of omalizumab or placebo plus immunotherapy. By the end of treatment, ragweed-specific IgG levels had increased by more than 11-fold in immunotherapy patients, while free IgE levels decreased by more than 10-fold in omalizumab recipients. Additionally, the incidence of adverse events (AEs) was lower in patients receiving omalizumab plus RIT than in those receiving RIT alone, and there was a 5-fold decrease in the risk of anaphylaxis due to RIT. Symptom severity scores were also significantly improved during the ragweed season in patients receiving omalizumab plus RIT, compared with RIT alone (0.69 vs 0.86; $p = 0.044$). Overall, these findings indicated that omalizumab could improve the safety of RIT for allergic rhinitis and may permit the use of more rapid and higher doses of allergen immunotherapy.

The combination of SIT and omalizumab was also more effective than either treatment alone in a study of 221 children and adolescents with SAR.[53] Patients received SIT or placebo along with omalizumab or placebo before and during pollen seasons for a total of 24 weeks. The combination of SIT and omalizumab reduced symptom load by 48% compared with SIT alone. Similar findings were reported from a study in 221 children and adolescents with allergic rhinoconjunctivitis.[54] Treatment with SIT before the pollen season did not improve symptoms or rescue medication use when used alone, but the concomitant use of omalizumab and SIT resulted in significant ($p < 0.001$) reductions in rescue medication use and the number of symptomatic days. More recently, results from a randomized, double-blind, placebo-controlled trial showed that omalizumab in combination with depigmented SIT reduced symptom load by 39% ($p = 0.0464$), compared with depigmented SIT alone, during the pollen season in patients with co-morbid seasonal allergic asthma and SAR.[55] This combination also improved asthma control and asthma-related quality of life.

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Other allergic conditions

Targeting IgE is a rational approach in the treatment of other IgE-mediated conditions other than asthma or rhinitis. Several studies showing that omalizumab had beneficial effects in patients with latex allergies[56,57] or peanut allergy[58] have been reviewed previously.[9] Recent case studies have also revealed encouraging outcomes in omalizumab-treated patients with allergic bronchopulmonary aspergillosis.[59–64] It has also been suggested that omalizumab may have potential benefits in patients with eosinophil-associated gastrointestinal disorders (EGIDs), which are often associated with atopy;[65] in 9 patients with EGIDs, treatment with omalizumab resulted in significant reductions in eosinophil counts and basophil and dendritic cell FcεRI expression, as well as significant improvements in symptom scores.[65] Several small studies and case reports have been published which indicate a potential benefit of omalizumab therapy in patients with urticaria. In one small proof of concept study in patients with chronic autoimmune urticaria (n = 12), 12 to 16 weeks following initiation of omalizumab, mean Urticaria Activity Score ($p = 0.0002$) and rescue medication ($p = 0.004$) use were significantly decreased, and quality of life was improved ($p < 0.05$).[66]

Anti-inflammatory activity

In addition to the effects of omalizumab on inflammatory mediator release from mast cells and basophils, and the down-regulation of FcεRI expression described earlier, the effects of omalizumab on several other markers of inflammation have been evaluated, with particular reference to effects on eosinophils in light of their prominent role in inflammatory responses.[5,24] In two studies, measurements of circulating blood eosinophils were made in patients with moderate-to-severe persistent asthma.[15,19] A pooled analysis found that omalizumab reduced mean peripheral blood eosinophil counts (LSM change from baseline -0.119×10^9/L; $p < 0.0001$), while there was no significant change in the placebo group.[67]

Omalizumab has also been shown to reduce sputum and bronchial eosinophilia in a study of 45 patients with mild-to-moderate persistent asthma and persistent airway inflammation.[23] At 16 weeks, reductions in mean percentage sputum eosinophil counts were significantly greater in omalizumab-treated patients (from 4.8% at baseline to 0.6% at Week 16) than in placebo recipients (from 5.8% to 2.3%; between treatment group difference: $p = 0.005$). Eosinophil counts in the bronchial submucosa also decreased from 8.0 cells/mm^2 at baseline to 1.5 cells/mm^2 at Week 16 in the omalizumab group ($p < 0.001$), but were almost unchanged in the placebo group. Omalizumab was associated with significantly greater reductions in FcεRI$^+$ ($p < 0.01$), CD3$^+$ ($p < 0.05$) and IL-4$^+$ ($p < 0.05$) cells in the epithelium and submucosa and in CD4$^+$ ($p < 0.01$) and CD8$^+$ ($p < 0.05$) cells in the submucosa. Observed reductions in CD3$^+$ ($p = 0.001$), CD4$^+$ ($p = 0.005$), CD8$^+$ ($p = 0.005$) T-lymphocytes and CD20$^+$ ($p = 0.02$) B-lymphocytes were also significantly greater in omalizumab recipients than in the placebo group. These findings have been confirmed in a study in 25 patients with mild allergic asthma.[27] The median sputum percentage eosinophil count was reduced from 4.0% at baseline to 0.5% at 12 weeks in omalizumab-treated patients, compared with an increase from 2.2% to 2.6% in the placebo group (between treatment group difference: $p = 0.003$). There was also a significant reduction in median activated eosinophil counts in biopsies in the omalizumab group (from 15.0 to 2.0 cells/0.1 mm^2), with little change in the placebo group (from 14.5 to 11.0 cells/0.1 mm^2; between treatment group difference: $p < 0.005$). Additionally, omalizumab-treated patients had significant ($p < 0.0001$) reductions in submucosal IgE+ cells compared with placebo and a significant ($p = 0.021$) reduction in CD4$^+$ T-lymphocytes compared with baseline. Taken together, these findings indicate that reductions in asthma exacerbations brought about by omalizumab may be mediated through attenuation of airway eosinophilia, while the reductions in IL-4$^+$ cells may be important in light of the documented association between persistent IL-4 production and severe or corticosteroid-resistant asthma.[23,68]

Several studies have provided information on other anti-inflammatory effects of omalizumab. Reductions in IL-13$^+$ lymphocytes and decreases in circulating eosinophil counts and IL-13, IL-5 and IL-8 levels were seen in a study of 35 patients with moderate-to-severe allergic asthma treated with omalizumab.[69] Th2 cytokines such as IL-4, IL-5 and IL-13 are believed to promote the recruitment and activation of mast cells and eosinophils.[68] In another study in 19 patients with moderate-to-severe asthma and a history of allergic rhinitis, 12 weeks of treatment with omalizumab resulted in significantly greater eosinophil apoptosis (60.1% Annexin-positive cells), compared with placebo (45.6%; $p = 0.004$).[70] No significant change in the marker 7-amino-actinomycin was seen, indicating eosinophil apoptosis rather than necrosis. This study also revealed a reduction in peripheral T-lymphocytes positive for granulocyte macrophage colony stimulating factor (GMCSF) (mean 10.5%), compared with placebo (12.1%; $p = 0.018$) and baseline (17.7%; $p = 0.0039$), and significant reductions in

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the IL-2+ and IL-13+ T-lymphocytes in omalizumab treated patients, compared with placebo (both $p = 0.027$). Omalizumab was also shown to reduce histamine release from basophils in a study of 17 patients with allergic asthma.[71] Reduction in maximal histamine release ($p < 0.01$) and cellular allergen sensitivity ($p < 0.05$) from baseline were significantly greater in the omalizumab group after 16 weeks of therapy compared with the placebo group, and there were corresponding changes in airway resistance, β_2-agonist use, skin prick tests, wheal area and the investigator's overall assessment of treatment effectiveness.

Anti-inflammatory effects have also been noted in studies of omalizumab in combination with SIT in patients with allergic rhinitis. For example, omalizumab plus SIT normalized myeloid dendritic cell numbers during the grass pollen season in children with SAR[72] and resulted in stable eosinophil cationic protein (ECP) levels and significant ($p < 0.05$) reductions in tryptase in a study of 225 children with a history of seasonal allergic rhinoconjunctivitis.[73]

Overall, there is compelling evidence that omalizumab has powerful anti-inflammatory effects in patients with allergic asthma and/or allergic rhinitis. Omalizumab has been shown to bring about substantial reductions in the activity of IgE, eosinophils, basophils, mast cells, and dendritic cells, resulting in attenuation of the acute and chronic effector phases of allergic inflammation.[74]

Safety of omalizumab

Safety in adults and adolescents

The safety of omalizumab has been evaluated in a pooled analysis of 7500 adult or adolescent (≥12 years of age) patients with asthma, rhinitis or related conditions who received omalizumab in clinical trials.[75] Overall, omalizumab had a good safety and tolerability profile and there was no evidence of an increased risk of malignant neoplasia or thrombocytopenia.

While omalizumab EU prescribing information includes a numerical imbalance in malignancies in the omalizumab group compared with the control group in pooled trials (0.5% and 0.18% respectively), the diversity in cancer type, short duration of exposure to omalizumab, and clinical features of individual cases makes a causal relationship unlikely[29]. Furthermore, a comparison of cancer rates from omalizumab clinical trials with the National Institutes of Health (NIH) Surveillance, Epidemiology and End Results (SEER) database found that the overall number of cancers reported in the omalizumab group was similar to that expected in the general population, while the number in the control group was one-third of that expected.[76] To December 2007, approximately 106,000 person-years of exposure to omalizumab have been achieved in the post-marketing setting, and only a small number of malignancies reported (120 cases, or 0.11 per 100 person years; author correspondence with Novartis, data on file).

In preclinical studies, a decrease in platelet counts was observed in cynomolgus monkeys at doses approximately 4 to 20 times higher than anticipated maximum clinical serum concentrations, and in clinical trials, a few patients had platelet counts below the lower limit of the normal laboratory range; however, none were associated with bleeding episodes or a decrease in hemoglobin. No pattern of persistent platelet decrease has been reported in humans, although isolated cases of idiopathic thrombocytopenia have been reported in the post-marketing setting.[29]

In clinical trials, omalizumab was associated with a low incidence of anaphylaxis (0.14% in omalizumab-treated patients and 0.07% in control patients). Post-marketing surveillance in approximately 57,300 patients treated during 2003 to 2006 has found that anaphylaxis after use of omalizumab occurred in approximately 0.2% of patients.[77] A review of clinical trial and post-marketing surveillance data between June 2003 and December 2005 was also conducted by Omalizumab Joint Task Force (OJTF) of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology Executive Committees.[78] This review found that 35 patients had 41 episodes of omalizumab-associated anaphylaxis out of a total of 39,510 treated patients, corresponding to a reporting-rate of 0.09%. Based on this observation, the OJTF has recommended keeping patients under observation for 2 hours after the first three omalizumab injections and for 30 minutes after all injections;[78] however, this advice is not mandatory and can be modified, based on the physician's clinical judgment after discussion of the risks with the patient.

In the total population of patients enrolled in controlled clinical trials, the incidence of AEs was similar between the omalizumab-treated patients and the control group, and most events were of mild to moderate severity.[75] The most frequently reported AEs were nasopharyngitis, upper respiratory tract infection and sinusitis; these and other individual AEs occurred with similar frequencies in the omalizumab and control groups.

Safety in children

The good safety profile of omalizumab observed in adults and adolescents is also observed in children. In a study of

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children with asthma, omalizumab was generally safe and well tolerated.[44] No serious treatment-related AEs were reported during the study and the overall frequency and distribution of AEs were similar in the omalizumab and placebo groups. Most AEs were of mild to moderate severity. This promising safety profile was maintained over 52 weeks following a 24-week extension to the study by Milgrom et al[79] with no new or more serious AEs reported. In the more recent 52-week evaluation of efficacy and safety of omalizumab in children, omalizumab showed no difference in the overall incidence of AEs compared with placebo over the duration of the study.[46] The most common AEs reported were nasopharyngitis, sinusitis and upper respiratory tract infection, and AEs were mostly (91%) of mild or moderate severity. No anaphylaxis to omalizumab occurred, and there were no cases of malignancies or thrombocytopenia in omalizumab-treated children.

Cost-effectiveness

The annual cost of treatment with omalizumab is higher than conventional asthma therapies; in their assessment of the use of omalizumab in Scotland, the Scottish Medicines consortium estimated the annual cost of omalizumab therapy to be £3,330–19,980 (approximately €4,900 to €29,500) in June 2007.[80] Therefore, consideration should be given to the cost-effectiveness of this therapy in patients with severe persistent allergic asthma. Several studies with varying methodologies have evaluated the cost-effectiveness of omalizumab.

In 3 analyses in patients with inadequately controlled, severe persistent asthma despite high-dose ICS plus a LABA,[81–83] a Markov cohort model was used to estimate the cost-effectiveness of adding omalizumab to standard asthma therapy and compared the cost of lifelong standard therapy with that of 5 years of omalizumab followed by lifelong standard therapy. Incremental cost effectiveness ratios (ICERs) were calculated as the difference in total costs between omalizumab and standard treatment per quality-adjusted life year (QALY). Importantly, these analyses accounted for the fact that omalizumab should be discontinued after 16 weeks in patients who do not respond to therapy. These studies found that add-on therapy with omalizumab resulted in ICER values of €56,091 (INNOVATE efficacy data applied to Sweden as the reference country),[83] €31,209 (ETOPA data applied to Canada),[81] €44,910 (INNOVATE data applied to the Netherlands)[82] and €26,694 (ETOPA data applied to the Netherlands).[82] In a review of these studies, Sullivan and Turk concluded that these ICER values indicated that omalizumab is cost effective at a willingness-to-pay value of €60,000.[84]

An analysis by Oba and Salzman, conducted from the perspective of third-party payers used assessed cost-effectiveness in terms of the daily cost to achieve defined outcomes.[85] The daily cost to achieve each additional day in which asthma was controlled was $523, while the daily cost of a ≥0.5-point increase in Asthma Quality of Life Questionnaire score was $378 (US$ values from 2003).[85] In their review, Sullivan and Turk noted that these measures of cost-effectiveness were more difficult to interpret than incremental costs per QALY as a guide to resourcing decisions.[84] They also noted that this analysis used data from a less severe patient population and did not take account of the patients' responses to omalizumab at 16 weeks.[84]

In another study, Wu et al showed that omalizumab provided an additional 1.7 quality-adjusted months at an incremental cost of US$131,000 over 10 years (corresponding to a cost-effectiveness ratio of US$821,000 per QALY gained), and concluded that omalizumab is not cost-effective for most patients with severe asthma.[86] However, as Sullivan and Turk note, the model of Wu et al was based on a population with severe asthma, but used data from patients with mild-to-severe asthma and remains to be validated in patients with more severe disease.[84] Additionally, one of the main components of this analysis was health-related quality of life, which is based on prediction of FEV_1. Omalizumab has little impact on FEV_1, which is not strongly related to QALYs, and the model may therefore not adequately capture the benefits of omalizumab.[84] Overall, data from patients with severe asthma indicate that the cost-effectiveness of omalizumab in treatment responders compares favorably with that of other biologic treatments for chronic disease.[84]

Experience in clinical practice

To April 2007, an estimated 68,000 patients with moderate-to-severe persistent allergic asthma have been treated with omalizumab in clinical trials and real-life practice. Several studies that have evaluated the use of omalizumab in clinical practice have revealed outcomes consistent with the results of the clinical trials programme. For example, one study in 147 patients treated in French practices showed that in patients with follow-up data of at least 5 months, there were 62% fewer exacerbations requiring OCS, 65% fewer emergency department visits and 29% fewer hospitalizations per year than in the year prior to omalizumab treatment.[87] The observed safety and tolerability of omalizumab was similar to that seen in clinical trials.

Real-life data have also revealed the steroid-sparing potential of omalizumab. Pooled data from surveys of UK

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and French clinicians was evaluated to examine the effects of omalizumab on maintenance OCS requirements in patients treated with omalizumab for at least 16 weeks for severe persistent allergic asthma.[88] Among the 173 patients included in the analysis, 97 were receiving maintenance OCS at baseline. Of these patients, 61.9% stopped or reduced their OCS treatment, with 18.6% stopping altogether. These findings have been confirmed in a larger pooled analysis of data from clinicians in France, the UK and Germany. In this analysis of patients who received omalizumab for at least 16 weeks (n = 411), 199 patients were receiving maintenance OCS at baseline. Of these, 55.3% stopped or reduced OCS dose and 21.1% stopped altogether.[89]

German real-life data in patients with severe persistent allergic (IgE-mediated) asthma (n = 280) has also shown reductions in exacerbations (82%), hospitalizations (78%), unscheduled healthcare contacts (81%), and daily (76%) and nocturnal symptoms (84%) after 6 months of omalizumab, compared with the (period-adjusted) year before treatment. Quality of life was also improved (increase in Mini-Asthma Quality of Life Questionnaire overall score from 2.9 to 4.5), and efficacy and tolerability were rated as excellent or good by the majority of physicians (82% and 95%) and patients (86% and 94%).[90]

Taken together, these data demonstrate that benefits observed in clinical trials translate well into real-life clinical practice, with clinically relevant decrease in asthma-related events, reduction or cessation of maintenance OCS use, reduction of daytime and night-time symptoms, and improvements in quality of life.

Future prospects for development of omalizumab

Liquid formulation

Omalizumab is currently formulated as a sterile, preservative-free, lyophilized powder and solvent. Once mixed, it can take in excess of 20 minutes for the powder to dissolve completely.[29] The development of a liquid formulation, which offers advantages in terms of convenience to the prescriber, is ongoing. The pharmacokinetics and pharmacodynamics of this liquid formulation of omalizumab have been compared with the current lyophilized formulation in an open-label, parallel-group study of 155 atopic but otherwise healthy adults.[91] Total omalizumab, free and total IgE, and safety were determined for 84 days post-administration, and blood samples were collected. As the 90% confidence intervals of the dose-adjusted AUC_{0-inf} and C_{max} mean ratios were between pre-specified values, pharmacokinetic (PK) bioequivalence was demonstrated. Pharmacodynamic (PD) parameters also showed that free IgE and total IgE were comparable between the lyophilized and liquid formulations. The two formulations were found to be bioequivalent, resulting in similar exposure to omalizumab. No serious AEs were reported during the study, and AEs were comparable between formulations.

Dosing table expansion

Treatment of patients with omalizumab is currently limited to patients with a baseline total serum IgE of ≤700 IU/mL and body weight ≤150 kg according to the omalizumab dosing table. A recent study used clinical trial data[15,16,31,35] alongside unpublished bioequivalence study data on omalizumab, free IgE and total IgE concentrations in a predictive check of omalizumab-IgE binding model. Model-predicted IgE levels correlated well with clinical outcomes from the same clinical trials to demonstrate their relationship, allowing exploration of doses and regimens for patients with free IgE or bodyweight values outside the current EU dosing table.[92] Ultimately, this approach may enable future treatment of patients who cannot receive omalizumab at present.

Disease modification

Analysis of data from the 28 week INNOVATE has shown that upon withdrawal of omalizumab, IgE levels return to baseline and symptoms re-emerge,[93] and the current recommendation is that omalizumab should be administered according to the dosing table in those patients who respond to therapy for as long as they continue to benefit. However, one small study in which patients received long-term omalizumab therapy suggests that prolonged treatment may have the potential to alter the course of asthma. Patients with allergic asthma (n = 18) received omalizumab for approximately 6 years before discontinuation of therapy.[94] Between 6 and 14 months after discontinuation, 13 of 18 patients' symptoms remained the same as, or had improved from, their symptoms during treatment. The majority were in a stable clinical condition and reported high quality of life, no increased nightly asthma attacks, no emergency visits and little or no increase in medication. Sensitivity to cat allergen peaked 4 months after discontinuation and subsequently decreased to levels less than in control patients, and non-reactive basophils were seen in 6 out of 14 patients at 12 months. Overall, these findings indicate that most patients had mild asthma 12 to 14 months after the end of prolonged treatment with omalizumab, with persistent down-regulation

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of basophil reactivity (and presumably mast cell reactivity) suggesting that treatment was exerting a long-term disease-modifying effect.

There is also emerging evidence that long-term treatment with omalizumab reduces IgE production towards normal (non-atopic) rates. A study used two versions of a PKPD model, one of which allowed variation in IgE production over time, while the other had a fixed IgE production rate. The estimated mean initial IgE production rate was 1840 μg/day. In control patients, IgE production appeared to increase slowly at an average rate of 3.6% per year, while in omalizumab-treated patients IgE production rate decreased and was projected to stabilize at 132 μg/day.[95]

Further insight into the potential disease modifying effects of omalizumab will be provided by the ongoing EXPLORE study, a randomized, multicenter, double-blind, placebo-controlled, parallel-group trial, which is examining the effects of 78 weeks of add-on omalizumab treatment on markers of airway inflammation and remodelling (number of subepithelial eosinophils, mast cells, $CD4^+$ T-lymphocytes and reticular basement membrane thickness) in patients with moderate-to-severe persistent allergic asthma receiving ICS and a LABA.

Conclusions

IgE is central to the pathophysiology of allergic asthma and related conditions such as allergic rhinitis, providing a strong rationale for the development of anti-IgE therapy for the treatment of these diseases. By binding to free IgE, omalizumab reduces the level of circulating free IgE by up to 99%, prevents IgE from attaching to mast cells and basophils, down-regulates FcεRI expression, and attenuates the inflammatory response to allergens. There is accumulating evidence to show that omalizumab reduces the activity of a variety of pro-inflammatory cells (including eosinophils, mast cells and basophils) and down-regulates release of pro-inflammatory mediators, thereby attenuating both the acute and chronic effector phases of allergic inflammation. In addition, the effects of omalizumab on antigen-presenting cells (dendritic cells) indicate that it may also block the sensitization phase, as well as the effector phase.

The benefits of this novel anti-inflammatory mechanism of action have been well documented in an extensive programme of clinical trials, including the INNOVATE study, which have shown that omalizumab reduces asthma exacerbations, severe asthma exacerbations, inhaled corticosteroid requirements, and emergency visits, as well as significantly improving asthma-related quality of life, morning PEF and asthma symptom scores in patients with severe allergic (IgE-mediated) asthma. Results from clinical trials have also been replicated in routine clinical practice, where considerable reduction in the need for maintenance OCS following omalizumab has been reported.

As it is difficult to predict which patients will respond to omalizumab, it is recommended in the EU that the physician's overall assessment should be used to identify responders after 16 weeks of therapy. This way, it is possible to target the treatment to the patients most likely to benefit. When treatment is directed at these responders, omalizumab has been shown to provide cost effective therapy for inadequately controlled severe persistent allergic (IgE-mediated) asthma.

Ongoing studies continue to evaluate the treatment benefits of omalizumab and guide therapy. Additionally indications are that omalizumab could benefit children with inadequately controlled moderate-to-severe persistent asthma, and clinical trials in this population show results which are consistent with those in the adult population. The potential for disease-modification in asthma is also currently being investigated, as is the use of omalizumab in other IgE-mediated conditions.

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