

Expert Opinion

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Omalizumab for pediatric asthma

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Importance to the field: Omalizumab is of proven efficacy in the treatment of severe allergic bronchial asthma and works through inhibiting the activity of IgE and the allergic immune mechanism IgE mediates. It has been demonstrated to be efficacious in children with asthma but is not approved by the FDA for use in children below 12 years of age.

Areas covered in this review: Omalizumab is a 95% humanized monoclonal antibody that binds to circulating IgE at the same site on the Fc domain as the high-affinity IgE receptor, FcεRI. This blocks the interaction between IgE and mast cells and basophils, thereby preventing the release of inflammatory mediators that cause allergic signs and symptoms.

What the reader will gain: From the review of the literatures and statements from the FDA, Genentec and Novartis, the reader will gain a better appreciation of the value of omalizumab in treatment of severe asthma and the current status of its reported side effects.

Take home message: Omalizumab is of proven efficacy in adults and children with severe asthma and allows a markedly reduced dependence on oral and inhaled corticosteroids and decreased hospitalizations. A potential mechanism of omalizumab's effect on thrombus formation and cardiovascular effect is postulated.

Keywords: allergic rhinitis, allergy, anti-IgE, asthma, cytokines, heparin, histamine, leukotrienes, mast cells and basophils, omalizumab, thrombus formation

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1. Introduction

Asthma is a chronic allergic disease of airways characterized by bronchial hyperresponsiveness [1]. It markedly diminishes quality of life due to limited activity, absences from work or school and hospitalizations with significant social and economic consequences. More than 20 million people in the USA and 300 million people around the world have been estimated to have asthma and one third of them are children [1]. Blacks and Porto-Ricans have higher morbidity and mortality [2,3]. Although most of the patients respond well to presently available drugs like beta adrenergic agonists and inhaled corticosteroid, nearly 5 to 10% do not respond and have severe disease. Patients with inappropriately controlled severe asthma are at higher risk of hospitalization and death and severely impaired quality of life [4-6]. The main initiator of the inflammatory cascade in the airways is IgE and plays an important role in the pathophysiology of asthma. An important unmet need is for a therapeutic agent that inhibits the allergic reaction upstream by decreasing IgE-mediated allergic reaction-. Omalizumab is the only agent currently available with this action (Box 1).

Omalizumab is a novel therapeutic approach in the treatment of asthma and has been approved by the FDA for the treatment of patients with moderate to severe persistent asthma and who are older than 12 years of age. Omalizumab is being studied for the control of allergic diseases (Figure 1) [7].

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Box 1. Drug summary.

Drug name	Omalizumab
Phase	Phase IV
Indication	Patients with moderate to severe persistent asthma (age > 12) having positive skin test and symptoms inadequately controlled with inhaled steroids
Pharmacology	95% humanized monoclonal antibody targeting IgE
Route of administration	Subcutaneous
Pivotal trials	[25,37-41]

1.1 Immunoglobulin E and its receptors

IgE is present at lower levels in plasma than other immunoglobulins and has a shorter half life. When exposed to allergen, plasma cells produce IgE under the control of the T_H2 subset of CD4⁺ T helper cells and the cytokines IL-4 and IL-13 [8]. IgE binds via the constant Fc region to specific high-affinity cell surface receptors (FcεRI). FcεRI is composed of an α-chain, β-chain and a pair of γ-chains that form an integral transmembrane complex. Although α-chain is responsible for binding IgE, the β- and γ-chains are also required for insertion of the α-chain into the membrane and for signal transduction. These receptors are mainly expressed on mast cell and basophils. They are also found on antigen-presenting cells such as cutaneous Langerhans cells and dendritic cells (Figure 2). FcεRI has a high affinity for IgE (K_a 10⁻⁹ to 10⁻¹⁰ M) and the half-life of cell-bound IgE on basophils is estimated to be 10 days [8].

The most dramatic effect of omalizumab is its ability to reduce levels of the high-affinity IgE receptor (FcεRI) on peripheral blood basophils by approximately 90% in a week and by 99% with longer treatment (Figure 3).

2. Mechanism of action

The mechanism of omalizumab action is incompletely understood. Unlike steroids, omalizumab does not improve bronchial hyperresponsiveness and does not have large effects on lung function. Omalizumab (rhuMab-E25, Xolair) is a humanized recombinant monoclonal anti IgE antibody of mouse origin that binds specifically to the Fc portion of the circulating IgE and by preventing its binding to receptors on basophils and mast cells [9]. Omalizumab (MW 150 kDa) contains 95% of human IgG1 antibody. Omalizumab binds to free IgE at the same site as the high affinity FcεRI receptor.

Omalizumab decreases serum IgE levels, inhibits early asthmatic response [10-12] and late asthmatic response [13] and causes downregulation of FcεRI receptors on basophils [10,14,15]. The binding site is the Cε3 domain of IgE made of six key amino acids that form a three-loop system (Figure 4). Cε3 is accessible only to free IgE but not to the

IgE bound to basophils and mast cells where it has no access as it is occupied by the FcεRI receptor. These two distinctive characteristics confer to this molecule low immunogenicity (because of the low content of murine components) and no complement-binding properties (because of the human part of the molecule) [16]. With IgE-mediated inhibition of antigen cross-linking there will be no activation of mast cells or basophils [17]. This mechanism is made possible by the spatial arrangement of the Fc of IgE composed of two heavy chains with binding sites for FcεRI, FcεRII (CD23), and anti-IgE symmetrically positioned along a central rotational axis through its two CH3 domains [12]. These three binding sites are situated in an overlapping manner, hence occupation of one of these sites precludes any of the other two from additional interactions due to conformational changes [18,19]. When there is binding of one CH3 domain to FcεRI this inhibits anti IgE from interacting with the other CH3 domain [20]. The reduction in receptor levels occurs since IgE binds and stabilizes FcεRI at the basophil membrane [21]. Signaling through FcεRI causes the synthesis and release of T_H2 cytokines IL4 and IL13 that are essential for maintaining allergic responses. Because omalizumab does not bind to the cell-surface IgE it prevents the FcεRI cross-linking which could lead to anaphylaxis.

2.1 Pharmacokinetics and metabolism of omalizumab

Omalizumab is approved for use by adults and children above 12 years with moderate to severe persistent asthma who test positive to airborne allergen and whose symptoms are ineffectively controlled with inhaled corticosteroids. The drug is administered subcutaneously once every 2 or 4 weeks. It has a bioavailability of 62% and reaches peak serum concentration within seven to eight days [22]. The long half life (19 – 22 days) of omalizumab is because of its slow removal by the hepatic reticuloendothelial system which is conferred by the IgG1 portion [23]. The potential delay of weeks before any appreciable activity is noted depends on the availability of IgE and the receptor to which it is bound. The efficacy of omalizumab does not differ if given subcutaneously or intravenously because both the routes cause a decrease in IgE levels [20,24]. After May 10, 2008, the company required that the drug be administered by a patient's health care provider, due to a risk of anaphylaxis. Previously, the drug could be self-administered.

2.2 Omalizumab corticosteroid-sparing effect, dosing and duration of therapy

In 546 allergic asthmatics, symptomatic despite inhaled corticosteroid, omalizumab therapy safely improved asthma control and allowed a simultaneous reduction in corticosteroid requirement [25].

The dose of omalizumab is calculated based on patient's body weight and the baseline serum IgE level. The dosage calculated results in neutralization of free IgE levels to levels < 5% at baseline (0.016 mg omalizumab/kg per

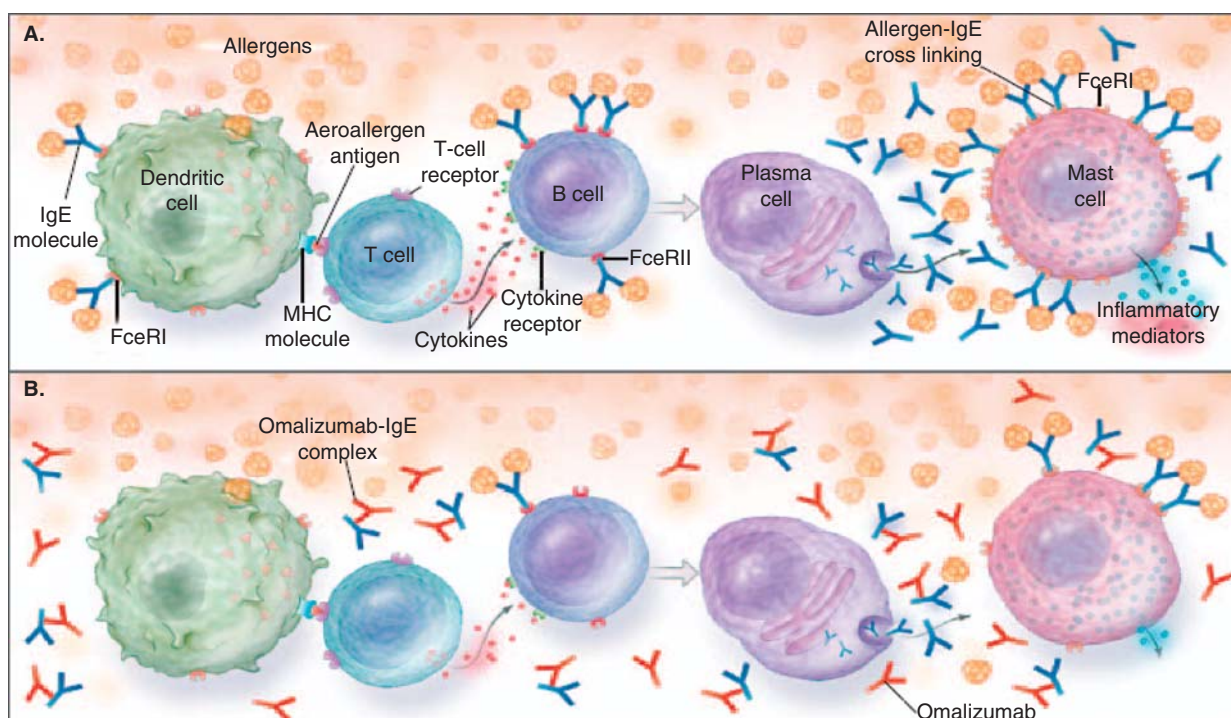


Figure 1. Pathophysiology of asthma. **A.** Aeroallergens initially interact with the immune system when they are taken up by dendritic cells. This process occurs by phagocytosis and may be enhanced after initial sensitization by the binding of allergen-specific IgE to high-affinity receptors (FcεR1) on the surface of dendritic cells. Dendritic cells process the allergen and present it, bound to MHC molecules, to T cells. T cells are stimulated by the interaction of MHC-bound antigen with surface T-cell receptors, causing T-cell proliferation and the subsequent release of cytokines. These cytokines stimulate B cells to become plasma cells that produce IgE. B cells express low-affinity Fcε receptors (FcεR2); interaction of IgE with these receptors may influence B-cell differentiation and regulation of IgE synthesis. IgE produced by plasma cells binds to the surface of mast cells and basophils and, when cross-linked by allergen, induces degranulation and the release of inflammatory mediators. This process results in FcεR1. This results clinically in an acute asthma attack. **B.** Omalizumab is a monoclonal anti-IgE antibody that binds to the Fc region of the IgE molecule. In so doing, omalizumab prevents IgE from binding to cell-surface receptors. Omalizumab is unable to bind to IgE molecules that are already bound, so it cannot induce anaphylaxis. Reduced binding of IgE to FcεR1 on mast cells and basophils inhibits degranulation and the release of inflammatory mediators. There is also marked downregulation of FcεR1. Reduced IgE binding to FcεR1 on dendritic cells may reduce the ability of these cells to process antigen efficiently. Reduced IgE binding to FcεR2 on B cells is thought to alter B-cell differentiation and the regulation of IgE synthesis. All these effects may contribute to the prevention of acute exacerbations of asthma [7].

IU/ml per 4 weeks). The IgE levels should not be measured after the beginning of treatment since the total IgE may actually increase secondarily to formation of omalizumab-IgE complexes. It is a long-term therapy administered subcutaneously every 2 – 4 weeks depending on body weight and base line IgE levels [26]. Omalizumab leads to decrease in unbound serum IgE by 84 – 99% within approximately 1 h after a single subcutaneous injection with low levels lasting from 4 – 6 weeks [22,27]. Each vial of omalizumab contains 150 mg of the drug. Some patients are excluded from administration of the drug because of high weight or because of levels of IgE > 700 IU/ml. The recommended monthly dose is equal to $0.016 \text{ mg} \times \text{body weight (kg)} \times \text{IgE levels (IU/ml)}$, and it may result in greater than 750 mg

(maximum monthly dose) (Table 1) [16]. It is important that correct doses of omalizumab in children be determined. Not all patients receiving omalizumab experience the desired clinical benefits. The treating physicians of these patients need to know whether the prescribed omalizumab dose has reduced free serum IgE levels in the therapeutic range (> 95%) [28].

However, we are not aware of a CLIA-88 licensed clinical laboratory to measure serological free IgE level in patients receiving omalizumab because documented serological assays are not available. Hamilton *et al.* have developed and validated a panel of free and total serum IgE immunoassays (IEMAs) specifically designed to evaluate the serum of patients on omalizumab [28].

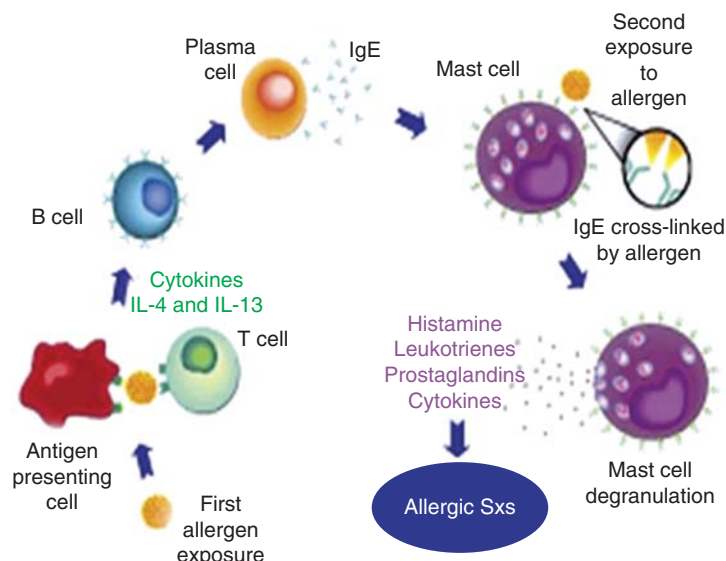


Figure 2. Immunoglobulin E and the allergic cascade. After allergen sensitization, cytokines stimulate B cells to produce allergen-specific IgE. Immunoglobulin E molecules then circulate and bind to high-affinity IgE receptors (FcεRI) on the surface of mast cells and basophils. Activation of mast cells and basophils by cross-linking of the surface IgE molecules leads to degranulation and release of mediators.

Adapted from [10].

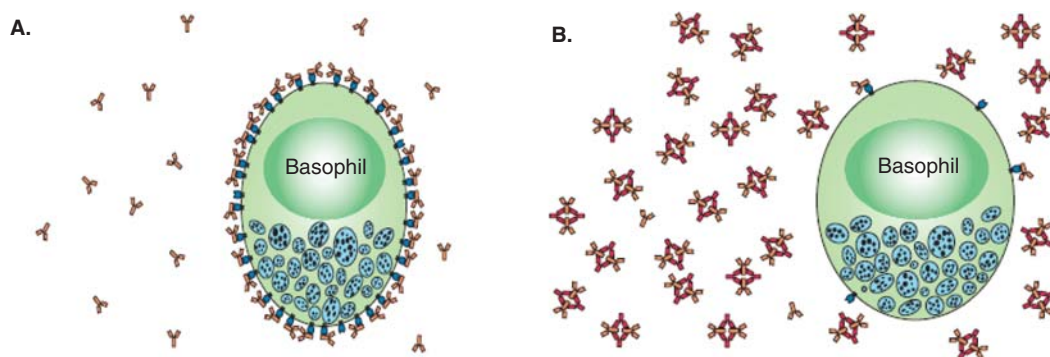


Figure 3. The effect of continual anti-IgE treatment on accumulation of IgE-anti-IgE immune complexes and the downregulation of FcεRI. A. Without anti-IgE treatment. B. With anti-IgE treatment [13].

2.3 Cost analysis

The cost of each vial of omalizumab is \$568 for a single dose of 150 mg. The lowest dose regimen is one 150 mg vial every 4 weeks which will cost \$616 per month and \$7,388 per year. Thus an average dose of omalizumab will be 300 mg every 4 weeks or 225 mg every 2 weeks depending on patients body weight [29]. It was concluded that omalizumab use could result in cost saving only if it is used in non-smoking patients who are hospitalized at least 5 times or 20 days per year or requires an emergency department visit every 7 months for treatment of asthma-related exacerbations [30]. Thus other authors also recommend that the use of omalizumab should be only for moderate-to-severe allergic asthma which is not

adequately controlled and requires frequent health care services for management of exacerbations [30-33].

2.4 Indications for omalizumab use

Some criteria for use of omalizumab that patients should fulfill are:-

- 1) A diagnosis of moderate-to-severe persistent asthma or high-risk patients, which are those patients who have frequent intubation, emergency room visits, overnight hospitalization and/or intensive care unit admissions for asthma exacerbations [34-36].
- 2) Age greater than 12 years.

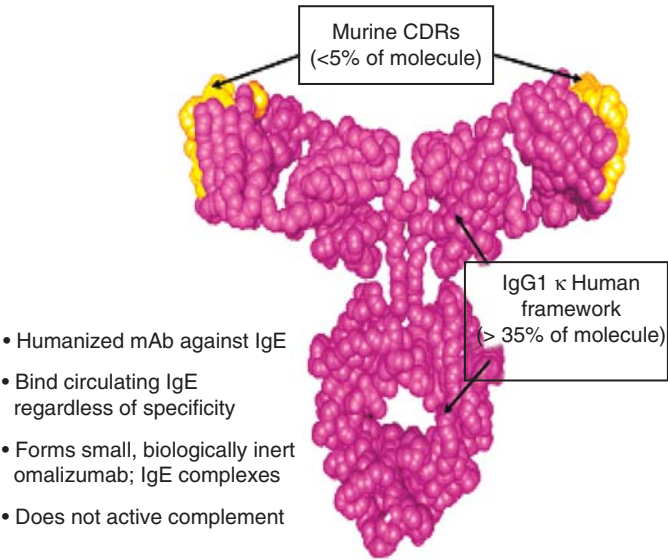


Figure 4. Omalizumab structure. Omalizumab is a recombinant humanized monoclonal antibody composed of 95% human sequence and 5% murine sequence.
Adapted from [21].
CDR: Complementarity-determining region.

Table 1. Recommended Xolair (omalizumab) dose (mg) according to patient body weight and baseline IgE level.

Base line IgE (IU/ml)	Body weight (kg)					Frequency of dosing
	30 – 60	> 60 – 70	> 70 – 80	> 80 – 90	> 90 – 150	
≥ 30 – 100	150	150	150	150	300	Every 4 weeks
> 100 – 200	300	300	300	300	225	Every 2 weeks
> 200 – 300	300	225	225	225	300	
> 300 – 400	225	225	300	300		Not dosed
> 400 – 500	300	300	375	375		
> 500 – 600	300	375				
> 600 – 700	375					

Xolair® prescribing information, Genentech, Inc. and Novartis Pharmaceutical Corp. 2003.

- 3) Serum IgE levels between 30 and 700 IU/ml.
- 4) A positive skin test or Radioallergosorbent test (RAST) for at least one perennial aeroallergen.
- 5) Body weight between 30 and 150 kg.
- 6) Symptoms with appropriate therapy after 1 – 2 month trial, that is after maximal maintenance therapy for severe persistent asthma using high dose inhaled corticosteroids (ICS) (> 800 µg/day becomethasone dipropionate, chlorofluorocarbon containing or equivalent) plus long-acting beta agonist plus oral corticosteroids.
- 7) Patient inhaler technique and adherence cannot be maintained despite adequate training and education having been maximized. Omalizumab is not approved for treatment of asthma exacerbations, such as acute bronchospasm or status asthmatics [20].

Different studies done by Soler *et al.* [25], Busse *et al.* [37], Humbert *et al.* [38] and Holgate *et al.* [39] concluded that omalizumab improves symptoms of asthma in patients resistant to steroid treatment or requiring excessive amounts of steroids for improvement of their symptoms. Vignola *et al.* [40] reported that omalizumab improves symptoms of both asthma and allergic rhinitis. A study by Kulus *et al.* [41] revealed that omalizumab is a safe drug in the pediatric group as well (Table 2).

2.5 Safety profile

The most common adverse effect is injection site pain and bruising but the package insert contains the ‘black box warning about anaphylaxis. It also includes warnings against malignancies and geohelminth infections. Patients receiving

Table 2. Summary of some important studies on omalizumab in patients with asthma.

Study n = number of patients	Patient age and baseline characteristics	Study duration	Type of study	Result: response rate with treatment versus control
[25] n = 546	Age 12 – 75 years BDP 500 – 1200 µg/day Patients with moderate to severe asthma	28 weeks SSP = 16 weeks SRP = 8 weeks MP = 4 weeks	Multicenter randomized double-blind placebo-controlled parallel group	SSP showed 58% and SRP 52% fewer exacerbations $p < 0.001$ Daily ICS dose 100 µg versus 300 µg, $p < 0.001$ ICS dose reduction by > 50% was 79 versus 55% of patients ICS complete withdrawal by 43 versus 19%
[38] n = 419	Age 12 – 75 years In patients inadequately controlled despite high dose ICS > 2300 µg/day and LABA	28 weeks	Randomized double-blind parallel-group multicenter	Clinically significant asthma exacerbation was 0.68 versus 0.91 $p = 0.042$ Severe asthma exacerbation showed 50% reduction Rate 0.24 versus 0.48 $p = 0.002$ Emergency visit rate was 0.24 versus 0.43 $p = 0.038$
[39] n = 246	Age 12 – 75 years Patients with severe allergic asthma Fluticasone dose of > 1000 µg/day	32 weeks 16 week steroid add on phase 16 week SRP	Randomized double-blind multicenter placebo-controlled trial	Median reduction in steroid dose 60 versus 50% $p = 0.003$ > 50% reduction in ICS 73.8 versus 50.8% $p = 0.001$ Reduction of < 500 µg/day in 60.3 versus 45.8% $p = 0.026$
[41] n = 246	Age 6 – 12 years Children with severe persistent allergic asthma ICS > 500 µg/day + LABA	52 weeks 24-week SSP 28-week adjusted steroid phase	Randomized double-blind placebo-controlled trial	In 24 weeks SSP reduction in asthma exacerbation by 34% versus placebo (0.42 versus 0.63) $p = 0.047$ By 52 weeks exacerbation rate was reduced by 50% $p < 0.001$
[37] n = 525	Age 12 – 75 years BDP dose 570 – 568 µg/day in treatment versus placebo group	28 weeks SSP 16 weeks SRP 12 weeks	Randomized double-blind placebo-controlled multicenter parallel group	Reduction in asthma exacerbation in SSP (0.28 versus 0.54 $p = 0.006$) SRP 0.39 versus 0.66 $p = 0.003$ BDP reduction 75 versus 50% $p < 0.001$ BDP discontinued in 39.6 versus 19.1% $p < 0.001$
[40] n = 405	Age 12 – 75 years Patients with moderate to severe asthma and persistent allergic rhinitis ICS > 400 µg/day IgE level of > 30 to < 1300 IU/ml	28 weeks Treatment with > 0.016 mg/kg/IgE(IU/ml) per 4 weeks	Multicenter Randomized double-blind placebo-controlled parallel group study	Reduced asthma exacerbation 20.6 versus 30.1% $p = 0.002$ AQLQ and RQLQ > 1.0 pt improvement in 57.7 versus 40.6% $p < 0.001$ Percentages of serious adverse events were 1.4 versus 1.5%

AQLQ: Asthma Quality of Life Questionnaire; BDP: Beclomethasone dipropionate; ICS: Inhaled corticosteroid; LABA: Long-acting beta 2 agonist; MP: Maintenance period; RQLQ: Rhinitis Quality of Life Questionnaire;
SRP: Steroid reduction phase; SSP: Steroid stable phase.

omalizumab injections commonly have local reactions such as bruising, warmth, erythema, swelling and urticaria like eruption. The local reactions are sometimes severe. Anaphylaxis can occur in 0.1% of injections. According to the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology Joint Task Force Report, 35 patients had 41 episodes of anaphylaxis associated with omalizumab corresponding to an anaphylaxis reporting rate of 0.09% of patients.

In a report by (Dreyfus *et al.* 2006) of Phase II/III clinical trial in allergic asthmatics where approx 6700 patients received omalizumab, the most common adverse reactions reported were pain, swelling, itching and erythema at the injection site and lasted for short period and were self limited. Anaphylaxis was reported with a frequency of about 0.1%. In one of these reactions it was possible to achieve tolerance to omalizumab by desensitization, however this was followed by serum-sickness-like disease [42].

Investigators at the FDA profiled omalizumab-associated anaphylaxis from June 2003 to December 2006 [43] among 57,300 omalizumab-treated patients 124 cases of anaphylaxis occurred. The calculated prevalence of these reactions was 0.2% and was higher than expected on basis of clinical trial data where 0.1% prevalence was noted. They also revealed that omalizumab-associated anaphylaxis might have a delayed onset in some cases, which can hinder determination of the cause of anaphylaxis [44].

Reduced platelet counts were observed in juvenile cynomolgus monkeys receiving higher doses of omalizumab than those used in humans. However there is no clinically relevant evidence that treatment with omalizumab causes a decrease in platelet count [45].

2.6 Omalizumab and malignancy

In the initial clinical trials a higher incidence of malignancies were seen in the group that received treatment with omalizumab (20 out of 4127 (0.5%)) than in the control group (5 out of 2236 (0.2%)) [46]. The majority (60%) of cases were diagnosed within 6 months of treatment. Overall the clinical data did not suggest a causal relationship between omalizumab and malignancy. Nevertheless the package insert of Xolair (omalizumab) contains a statement that 'the impact of longer exposure to Xolair use in patients at higher risk of malignancy is not known' [46]. Data analysed from 35 Phase I, II and III multiple-dose studies of omalizumab showed that 25 out of 5015 patients (0.50%) reported malignant neoplasms compared with 5 out of 2854 (0.18%) controls patients. Malignant neoplasm was reported in the majority of these patients during the first 52 weeks of treatment 20 of 25 (80%) omalizumab-treated and 5 of 5 (100%) control patients. Those diagnosed after 52 weeks or more of omalizumab treatment were parotid gland cancer at 59 weeks, pancreatic cancer at 61 weeks, sigmoid and prostatic cancer at 99 weeks, and basal cell cancer at 119 weeks [45].

In an observational cohort study titled Evaluating the Clinical Effectiveness and Long term Safety in Patients with moderate to severe Asthma (EXCELS), which includes nearly 5000 patients with moderate to severe asthma treated with omalizumab and 2500 with moderate to severe asthma not treated with omalizumab, the 95% confidence interval suggests that the incidence of cancer is not statistically significant and the result could be due to chance [46].

2.7 Omalizumab and parasitic infection

Parasitic helminth infections cause the production of IgE, which has a protective role in the immunity against parasitic infections. Thus it is theoretically possible that omalizumab could increase susceptibility to helminth infections. Thus the Xolair (omalizumab) package insert recommends that patients who are at high risk for parasitic infections should be monitored closely during the course of treatment.

A 52 week randomized double-blind placebo-controlled (DPBC) study in 137 patients at high risk of geohelminth infections were randomized to receive treatment with omalizumab or placebo. Of the patients in the omalizumab group 50% (34 out of 68) were found to have at least one geohelminth infection compared with 41% (28 out of 69) of patients in the placebo group. The odds ratio adjusted for study visit, gender age, and baseline infection status was 2.2 (0.94 – 5.15), $p = 0.035$. There is no increased morbidity in response to clinical adverse events in omalizumab-treated patients compared with the placebo group. These studies suggest that people at high risk of parasitic infections may be at a greater risk with omalizumab treatment but the severity and response to treatment are similar to those of placebo treated patients [46].

2.8 Pregnancy

The safety and efficacy of omalizumab in pregnancy has not been determined. Theoretically anti IgE should not be harmful to the fetus and may be advantageous. Reproduction studies done in cynomolgus monkeys by giving them 12-times the maximal dose given in humans and injecting 75 mg omalizumab/kg subcutaneously. It was found that there was no maternal toxicity, teratogenicity or embryotoxicity in the monkeys when the drug was administered throughout late gestation, during delivery or nursing. The data of these studies indicate that there is no troublesome effect of treatment with omalizumab on pregnancy outcome. However its use in pregnancy cannot be advised since there are not sufficient clinical studies of the effects of omalizumab on pregnancy outcome. Omalizumab has been classified by the FDA as pregnancy category B. There is an ongoing observational study, the EXPECT registry of omalizumab effect on pregnancy outcome and safety. This study includes patients who have been exposed to omalizumab during pregnancy and within 8 weeks of conception [45].

2.9 Effect of omalizumab in children

Asthma is the most common chronic illness of children and has increased considerably over the past decade. A 75% rise in between 1980 and 1994 in the USA has been reported. A study was performed by Milgrom *et al.* which was a multicentre randomized double-blind, placebo-controlled, parallel-group 28-week trial which was done primarily to evaluate the safety and efficacy of omalizumab in children with moderate to severe asthma [47]. It was done in 334 children aged 6 to 12 years with moderate to severe asthma requiring inhaled corticosteroids as treatment. A total of 225 children were in the omalizumab group and 109 were in the placebo group. Beclomethasone Dipropionate (BDP) was kept stable for 16 weeks (stable steroid phase) then reduced over 8 weeks to the minimum effective dose (steroid reduction phase), and maintained constant for final 4 weeks. It was found that BDP dose was decreased in more children treated with omalizumab than in the placebo group, with a median reduction of 100 versus 66.7%. In 55% of the omalizumab-treated children BDP was withdrawn completely versus 39% in the placebo group. Children in the omalizumab group experienced fewer asthma exacerbation episodes (18.2%) than those on the placebo (38.5%). Five children required hospitalization for asthma exacerbation, all in the placebo group. At 28 week the median number of puffs of rescue medication taken daily was found zero in the omalizumab treated children and 0.46 in the placebo group. The mean number of unprepared medical visits due to asthma-related problems throughout the treatment period was less in the omalizumab group than the placebo group (0.15 versus 5.35). Hence treatment with omalizumab can be well tolerated by children and there are no major adverse reactions or events. Those that occurred were mild to moderate in intensity, 6.2% in the omalizumab treated versus 0.9% in the placebo group. There were no immunologic or immune complex related adverse event and those noted were mild to moderate urticaria. The adverse reaction reported in the omalizumab group were similar to those for the placebo group. Thus it can be concluded that treatment with omalizumab is safe and well tolerable in children with Asthma [47].

In a separate study by Lanier *et al.* reported that omalizumab is effective therapy in children (6 to < 12 years) with moderate to severe persistent allergic asthma [48]. In these children whose symptoms are not adequately controlled despite treatment with medium-to-high-dose ICS. They studied total of 725 patients who were randomized, with efficacy analyzed in 576. In the 24-weeks fixed-steroid phase, the rate of clinically significant asthma exacerbation was reduced by 31% versus placebo ($p = 0.007$). There was no difference in overall incidence of adverse events in omalizumab-treated group compared with the placebo group over a period of 52 weeks. Most adverse events were mild to moderate in severity. The incidence of serious adverse events were lower in omalizumab-treated group compared with the placebo group (4 versus 8%; $p < 0.05$) [48].

2.10 Churg-Strauss syndrome

Churg-Strauss syndrome (CSS) may develop in patients who have an underlying eosinophilic disorder that is unmasked by withdrawal of corticosteroid therapy in patients with asthma. CSS is very uncommon in children as reviewed by Boyer *et al.* and these authors did not report any CSS in children undergoing omalizumab therapy [49]. In a paper by Wechsler *et al.*, CSS symptoms were reported in 8 of 13 (37 – 81 years of age) definite or probable cases prior to receiving omalizumab or just after corticosteroid weaning [50]. This data was based on patient exposure to omalizumab of approximately 87,500 person-years. Their data and from the literature suggest that a casual relationship between omalizumab and CSS is unlikely. However, clinicians should be aware of the signs and symptoms of CSS in asthmatic patients while corticosteroids doses are tapered and physicians should be conscious regarding development of vasculitis and/or infiltration of extrapulmonary tissue eosinophilia which is important in distinguishing CSS from eosinophilic asthma.

Kamin *et al.* studied patients with seasonal allergic rhinitis (SAR) receiving specific immunotherapy (SIT) to determine if omalizumab can significantly enhance the activity of SIT [47]. This study was a randomized double blind, placebo controlled multicentre trial in which 221 children were randomly assigned to four different groups and treated with SIT starting 14 weeks before the local birch pollen season. After 12 weeks either omalizumab or placebo treatment was added to the SIT therapy which lasted 24 weeks. Omalizumab and SIT combination was tolerated (82%) and the adverse reactions were only mild to moderate. Severe adverse reactions occurred in four patients in the placebo group. Thus it can be concluded that omalizumab can be considered in management of allergic diseases and is safe in children [51].

3. Regulatory affairs: omalizumab and cardiovascular, cerebrovascular effect

FDA issued a statement on July 16, 2009 on the review of the EXCELS study interim safety data which showed an increased number of cardiovascular and cerebrovascular adverse events in a group of patients receiving treatment with omalizumab compared with the patients not receiving the drug as a control group (see later for further details).

4. Conclusion

Omalizumab effectively blocks the interaction between IgE and mast cells and basophils. Omalizumab is of proven efficacy in patients with moderate and severe allergic asthma. It has been demonstrated to be effective and safe in children with asthma but is not approved by the FDA for use in children under 12 years of age. It also reduced the requirement for inhaled and oral corticosteroids and decreased

hospitalizations. Until the EXCELS study is completed patients as informed by the health care provider should be aware of the risks and benefits described in the prescribing information.

5. Expert opinion

Omalizumab is the only drug available for the treatment of patients with moderate or severe asthma that is not controlled with existing therapy including high dose inhaled corticosteroids and who require frequent hospitalization and oral corticosteroids. Omalizumab affects current treatment strategies by its control of asthma symptoms and the significant decrease in need and frequency of rescue bronchodilators and inhaled or oral corticosteroids. It is also likely to improve the effect and safety of allergy immunotherapy in allergic asthma and co-existent allergic rhinitis. Physicians are likely to prescribe omalizumab when they are fully aware of its effectiveness in severe asthma in patients who are not controlled with existing modalities.

The dosing regimen is based on the patient's serum IgE level and body weight. Thus, a limiting factor that precludes its use is the dose range in patients whose IgE or body weight is too high. Other factors are cost and the fact that it is not yet approved for children who are under age 12 years. The manufacturer should be able to improve and increase the production and increase the dose range of IgE above 700 IU and decrease the cost. The data from Phase III clinical trials in children show that it is safe and effective and in our opinion its benefit:side effects ratio is positive.

The cardiovascular thrombotic events have raised concern about prescribing omalizumab in children because of possible long-term side effects in children who may need omalizumab for many years. Genentech has provided data to the FDA that these cardiovascular and thrombotic events are attributable to more severe asthma and more co-morbidities in the omalizumab arm of the EXCELS study. With these factors in mind there is not a statistically significant increase in cardiovascular thrombotic events. The FDA is evaluating this data.

The EXCELS study is an observational study of 5041 omalizumab-treated patients and a control group of approximately 2886 non-omalizumab-treated patients with bronchial asthma. This is a 5-year observational study and the study population are subjects with moderate to severe persistent asthma of 12 years of age and older and who have a positive allergy skin, or blood aeroallergen tests. The initial report was in July 2009, and suggested a disproportionate increase in ischemic heart disease, arrhythmias, cardiomyopathy and cardiac failure, pulmonary hypertension, cerebral vascular disorders, and embolic, thrombotic and thrombophlebitic events in patients treated with omalizumab compared with the control group of patients not given the drug.

Since this is an interim analysis of the 5-year study, the FDA is not recommending any changes to the prescribing information for omalizumab and is not advising patients to

stop taking omalizumab at this time. However the approval for children under the age of 12 has been deferred. Genentech, the manufacturers of omalizumab, submitted the data and until the evaluation of the EXCELS study is completed, patients as informed by their healthcare providers should be aware of the risks and benefits described in the prescribing information as well as the new information from the ongoing EXCELS study. The FDA is working closely with Genentech to obtain further information and will continue to review the strengths and limitations of the interim results. It should be emphasized that since EXCELS is an observational study, there could be clear differences in the underlying risk factors for cardiovascular and cerebrovascular events between the study groups. People on omalizumab would have a more severe form of asthma and could have a number of co-morbidities that could contribute to the excess incidence of cardiovascular and thrombotic events. The results are expected in 2012. It is suggested that healthcare professionals and patients report side-effects to the FDA's Med. Watch Adverse Event Reporting Program. The interim analysis provided by Genentech to the FDA does not mean the FDA has concluded that there is a causal relationship between the drug products and the emerging safety issue. The FDA is not advising healthcare professionals to discontinue prescribing these products. The FDA will update this report when additional information of the analysis becomes available.

5.1 Endogenous heparin

Regardless of the outcome of the decision by the FDA, it would be important and informative to determine the effect of omalizumab on endogenous heparin and heparin-like molecule release in allergic asthmatic subjects because of the possible consequence in thrombotic cardiovascular events.

The presence of endogenous circulating heparin has been reviewed [52] and confirmed by other investigators [53,54]. Heparin acts as a specific blocker of inositol 1,4,5-triphosphate (IP3) receptors and inhibits IP3-mediated calcium release in cells including vascular smooth muscle, liver cells and airway smooth muscle [55,56]. Heparin has been reported to have non coagulant, anti inflammatory properties as well as regulating the activity of mast cell tryptase [57].

Heparin also attenuated the bronchoconstrictor response and the immediate cutaneous reaction to antigen in allergic sheep [58]. Heparin inhibits the immediate response to the antigen in skin and lungs of allergic subjects [59]. Inhaled heparin also prevented exercise-induced asthma [60]. From the above study, it appears that heparin may have beneficial effects in allergic asthma and its effects appear to be independent of its anti-coagulant activity.

5.2 Omalizumab inhibits mediators, cytokine and chemokine release

Oliver and colleagues very recently reported reduced FCERI-mediated release of asthma-promoting cytokines and

chemokines from human basophils during omalizumab therapy. The anti-IgE stimulated release of IL-4, IL-8, IL-13 and regulated upon activation, normally T-expressed, and presumably secreted (RANTES), was markedly reduced during omalizumab treatment [9].

5.3 Histamine release

An important characteristic of basophils from allergic asthmatics is a significant spontaneous histamine release (SHR) compared with basophils from non atopic subjects. Basophil SHR in patients with asthma not receiving asthma medication was significantly higher than in patients with asthma receiving medication. Basophils from subjects with asthma contain significantly less histamine than basophils from normal subjects [61]. High SHR was originally reported in persons hypersensitive to food. The data indicated that sensitivity to foods or exercise does not appear to be essential for high SHR. SHR from normal non-atopic subjects was always less than 10% of the total histamine. The overall result in normal subjects and not receiving asthma medication indicates an inverse relationship between SHR and histamine content. The SHR in subjects with asthma not receiving medication was significantly higher than SHR in asthma subjects receiving asthma medication.

5.4 Heparin release

There is a plethora of studies on histamine release and the effect of therapeutic agents in allergy and asthma on inhibiting histamine release, surprisingly there is relatively little information on heparin release. A very recent report on endogenous heparin levels in controlled asthmatic patients found the blood of the 53 asthma patients contained significantly lower levels of endogenous heparin compared with blood from 26 healthy individuals. The authors concluded the anti-inflammatory properties affected by heparin are diminished in the asthma patients [62]. This study is contrary to earlier studies by Lasser *et al.* reporting heparin-like anticoagulant in asthma to be significantly higher than in non-allergic, non-asthmatic controls. They reported that 22 asthmatic subjects had a mean heparin-equivalent (EHM) of 0.055 ± 0.035 U/ml versus 0.001 ± 0.00 in 29 control subjects. The plasma of the majority of asthmatic subjects contain between 0.006 and 0.5 U EHM/ml. Three of six asthma patients responded to inhalation antigen challenge with an acute increase in plasma heparin (EHM) that coincided with a fall in pulmonary function [63]. In individuals with a definite negative history of allergy, venous heparin had not been detected.

In animal studies immunologically induced mast cell activation resulted in degranulation with a parallel release of histamine and heparin [64]. This is analogous to a study in human basophils as reported by Tanizaki *et al.* These authors measured the release of heparin-like substance and histamine from basophilic leukocytes separated by counter-flow centrifugation elutriation [65]. They studied

histamine from basophilic leukocytes in healthy and asthmatic subjects. The content of histamine paralleled the number of basophils in each fraction. The release mechanism of histamine by anti-IgE was similar to that of the heparin-like substance. Release of histamine and heparin-like substance was significantly higher in atopic asthmatics than non-atopic subjects. The viability of basophils was greater than 95%. The maximum histamine release induced by anti-IgE was $36.6 \pm 11.1\%$ in patients with atopic asthma and $13.6 \pm 8.1\%$ in cases with non-atopic asthma. The maximum release of heparin like substance was 0.078 ± 0.053 U/ 10^5 basophils in atopic asthmatics and 0.035 ± 0.021 U/ 10^5 basophils in non-atopic asthmatics and 0.026 ± 0.028 U/ 10^5 basophils in healthy subjects. A significant difference was present in the release of heparin-like substance and histamine between atopic and non-atopic asthmatic subjects. The results demonstrated that histamine and heparin-like substance which was contained in the granules of the cells, were released similarly when the cells were challenged with anti-IgE.

In summary, the above studies are consistent with the observation that atopic, allergic asthmatics with increased IgE would release more histamine and heparin on exposure to allergens and could predict future non-fatal myocardial infarction but not fatal myocardial infarction in men [66]. Thus lowering the serum IgE and potentially decreasing the serum levels of histamine and heparin-like substances in patients with severe asthma could have untoward effects on thrombotic episodes including myocardial infarction.

On the possibility that these cardiovascular and thrombotic adverse events are related to the use of omalizumab we can speculate on possible mechanisms whereby this can occur. It is well known that mast cells produce heparin and basophils produce a heparin-like substance. Omalizumab reduces the number of IgE receptors on mast cells and basophils and decreases the amount of mediator and cytokine release including histamine and leukotriene following stimulation with allergen in these allergic asthmatic subjects. Heparin is contained in the granules of mast cells in tight binding with histamine. Therefore, the activation of mast cells and basophils by allergen would result in histamine and heparin release. Contrary to this, omalizumab should inhibit release of these mediators by markedly decreasing serum IgE and decreasing the IgE receptors on basophils and mast cells. Hence, one could speculate that the decreased endogenous heparin could conceivably result in increased thrombus formation. Indeed, endogenous heparin has been reported to be a protective marker in patients with myocardial infarction [67]. The aim was to study and evaluate whether there was a relationship between serum IgE levels and plasma concentrations of endogenous heparin in patients with myocardial infarction. The authors also attempted to analyze whether there is a relationship between the endogenous heparin plasma concentration and the specific markers (thrombin-antithrombin) complexes for the genesis of thrombi. They studied 35 healthy volunteers and 64 hospitalized patients with recent

myocardial infarction, ages 37 – 70 years. Subjects with a negative allergic history were excluded. Thrombin-antithrombin complexes in plasma were measured by ELISA and endogenous heparin plasma levels by Coatest heparin. This was measured at the time of admission and before treatment. They observed a significant difference in heparin concentrations in patients with MI compared with the control group. Higher levels of IgE were strongly correlated with higher concentrations of endogenous heparin ($R = 0.8$, $p < 0.001$). There was a strong and significant negative correlation between higher endogenous heparin and thrombin complexes ($R = -0.57$, $p < 0.001$). The results suggest that high concentrations of endogenous heparin is associated with high IgE concentrations and the inhibitory influence on thrombogenesis and was considered to be a marker of a favorable prognosis in patients with MI.

It was reported by Szczeklik *et al.*, that patients with myocardial infarction (MI) had a more favorable course and fewer complications and a significantly higher concentrations of serum IgE compared with those patients who either died from sudden cardiac arrest or had more or frequent severe complications [68]. They also reported that high levels of serum IgE correlated with a delay in thrombin generation during blood coagulation. These authors suggested that this might protect against sudden cardiac arrest. In a separate study by Langer *et al.* [66], it was reported that a protective role was associated with elevated concentrations of IgE in patients with MI who were observed for non-fatal myocardial infarction. The age-adjusted mortality risk for coronary artery disease in men with baseline IgE greater than 200 IU/ml was 1.66, which was not significant ($p = 0.66$). However, the mortality risk for non-fatal myocardial infarction was

6.46 ($p < 0.01$). They further reported that this association was independent of smoking and other risk factors and unrelated to allergy. This inverse association between IgE and coronary disease was seen in men but not in women. They followed 278 men and 343 women for a mean of 8.9 years. The study was part of a community-based population study. This study followed an earlier study by Szczeklik which concluded that high IgE was associated with survival among men with myocardial infarction (MI).

In the report by Langer *et al.*, the risk ratio for men with IgE levels of 200 IU/ml had a proportional hazards of non-fatal MI was 7.3, p value was 0.003, after adjustments for cigarettes per day, diastolic blood pressure, LDL cholesterol and fasting plasma glucose. The unique feature of non-fatal MI was apparent in this IgE association [66]. However, this cohort of 621 men and women was defined in a study of peripheral arterial disease. However, having peripheral arterial disease itself is a risk factor for coronary artery disease and must be considered in evaluating this study. The unique feature in association of IgE was only for non-fatal myocardial infarction events. There is no association between IgE and fatal myocardial infarction. This suggests that IgE-related events may involve the coronary microvasculature or perhaps local thrombosis, rather than chronic atherosclerosis.

Declaration of interest

The authors have performed two investigator initiated studies of Omalizumab in asthma and ragweed allergic rhinitis. RG Townley has also participated in two multicenter clinical trials of Omalizumab sponsored by Novartis and Genetec. S Agrawal and K Sapkota have nothing to disclose.

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