

EXPERT OPINION

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Omalizumab for treatment of allergic rhinitis

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Introduction: Immunoglobulin E (IgE) is a key pathogenic factor of allergic rhinitis, a prevalent disease adversely affecting quality of life and productivity.

Areas covered: Binding of inhaled allergens to IgE on the surface of basophils and mast cells, with subsequent cross-linkage of IgE and aggregation of high-affinity receptors for IgE (FcεRI), triggers the release of inflammatory mediators, followed by the onset of allergic rhinitis symptoms. Current therapeutic strategies include corticosteroids, mast cell stabilizers, leukotriene receptor antagonists, anticholinergics, antihistamines and allergen immunotherapy. Removal of circulating free IgE by the recombinant humanized monoclonal anti-IgE antibody, omalizumab (Xolair), represents a novel therapeutic approach. Omalizumab selectively binds to the Cε3 domain of IgE at the site of FcεRI binding, thus blocking binding of IgE to effector cells. We review omalizumab's clinical efficacy, administration, use with immunotherapy and safety in allergic rhinitis.

Expert opinion: Omalizumab may provide a new treatment strategy for allergic rhinitis. The high cost of omalizumab precludes its chronic use for allergic rhinitis and it is not FDA approved for this indication; however, its periodic use may be justified in treatment resistant patients, especially those with seasonal disease.

Keywords: allergic rhinitis, anti-IgE, IgE, omalizumab

Expert Opin. Biol. Ther. (2013) 13(6):933-945

1. Introduction

1.1 Allergic rhinitis

Although perceived as trivial or 'inconvenient', allergic rhinitis (AR), commonly called as hay fever is a major chronic respiratory disease with high prevalence [1]. It occurs in approximately 20% of the general population in the USA with some studies reporting a prevalence of up to 40% [2,3]. The disease is as old as mankind and the prevalence has increased over the years from the subtle interplay of societal and environmental factors along with genetic and immune system alterations [4].

For people with AR, quality of life can be considerably reduced, leading to impaired performance of daily activities, cognitive function and classroom productivity, and reduced psychosocial wellbeing [4]. Poorly controlled AR may be associated with various complications and comorbid conditions. AR and asthma frequently coexist, and AR usually precedes and is a significant risk factor for asthma [1,5,6]. Furthermore, evidence shows that treating AR can reduce asthma-related emergency department visits and hospitalizations [7].

AR was originally classified based on the timing of allergen exposure-seasonal or perennial. It can also be classified according to the duration of symptom presentation as intermittent or persistent [1]. The severity can be mild, moderate or severe depending on the impairment of sleep, daily activities, sports, school or work.

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Box 1. Drug summary.

Drug name	Omalizumab
Global phase	Launched
Indication	Rhinitis, allergic, seasonal, no development reported
Pharmacology description	Immunoglobulin E inhibitor
Route of administration	Injectable
Chemical name	Immunoglobulin G, anti-(human immunoglobulin E Fc region) (human-mouse monoclonal E25 clone pSVIE26 γ -chain), disulfide with human-mouse monoclonal E25 clone pSVIE26 κ -chain, dimer
Pivotal trial(s)	[59,61,64]

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1.2 Pathophysiology: role of immunoglobulin E and high affinity immunoglobulin E receptors

AR is a symptomatic disorder of the upper airways induced by inflammation caused by immunoglobulin E (IgE)-mediated effects in the membrane lining the nose after allergen exposure [8]. Allergic individuals become sensitized by producing IgE antibodies against allergens such as pollen, dust mites, animal dander and mould spores. Antigen-specific IgE binds to high-affinity receptors (Fc ϵ RI) on tissue mast cells, basophils and dendritic cells. On further exposure to the specific allergen, antigen binds to IgE antibodies on mast cells and basophils leading to cross-linking of two adjacent IgE molecules. This initiates intracellular signaling pathways and degranulation occurs leading to release of pre-formed and newly generated mediators and cytokines. This type I hypersensitivity is central to the pathogenesis of AR (Figure 1).

1.3 Early and late phase response

The immediate allergic response to antigen is termed the early phase response. The mediators released during this phase include histamine, kinins, neutral proteases, prostaglandins and leukotrienes [9-11]. Together, these mediators result in characteristic symptoms of AR-watery rhinorrhea, sneezing and itching-within minutes of allergen exposure (Figure 1).

This is followed several hours later by the late phase response, involving the infiltration of inflammatory cells due to cytokine and chemokine release from the mast cells. The subsequent release of mediators into the nasal mucosa from the basophils and eosinophils manifests as symptoms of early phase along with significant congestion and inflammation (Figure 1) [8].

2. Overview of the market

2.1 Currently available therapies

Control of symptoms, preventing inflammation and improvement of patient's quality of life are the primary goals of pharmacotherapy of AR. Presently, different major classes of drugs available for the treatment of AR are: antihistamines, corticosteroids, antileukotrienes, decongestants, mast cell stabilizers and anticholinergics [12-15]. First generation H₁-antihistamines are widely available over-the-counter, effective and economical.

However, their usefulness is limited by their potential to induce sedation due to significant penetration into the brain, leading to drowsiness and performance impairment [12,16,17]. Current recommendations are that only non-sedating second generation antihistamines be used [12]. Intranasal formulations of second generation H₁-antihistamines are also effective, and there is now a combination product containing an intranasal antihistamine and corticosteroid. Intranasal formulations of corticosteroids are by far most effective and the first-line therapy for the treatment of persistent or moderate to severe AR [15,18]. Prolonged use has rarely been associated with inhibition of growth in children, disturbances of metabolism, skin thinning and osteoporosis [12].

Antileukotrienes, specifically montelukast, are considered safe and effective for use in prophylaxis and therapeutic treatment of airway allergy. Montelukast has been shown to reduce the symptoms of AR [15,19].

Nasal decongestants-, α 1 agonists, are very useful in reducing nasal congestion; however, they have no effect on sneezing, pruritus, rhinorrhea and ocular symptoms. Intranasal decongestants have rapid onset and fewer systemic side effects. However, overuse of these agents causes rebound congestion and rhinitis medicamentosa [20]. Oral decongestants provide better relief of nasal congestion than antihistamines alone, but side effects can be problematic.

Other topical agents include intranasal cromolyns which have been shown to inhibit both early- and late-phases of AR. When used prophylactically, they can prevent as well as treat the symptoms of AR [21]. Topical anticholinergics like ipratropium bromide are beneficial for the treatment of rhinorrhea, without benefit on other symptoms of AR [22,23].

Allergen immunotherapy causes allergen-specific desensitization and has long-lasting immunotolerogenic effects. Different routes including subcutaneous, sublingual and oral are used to administer immunotherapy [13,24].

2.1.1 The step wise medical approach to treating AR is shown in Figure 2

Nasal irrigation with saline or hypertonic saline has been used in the complementary management of AR [25]. Other treatments which have been found to be useful for AR include

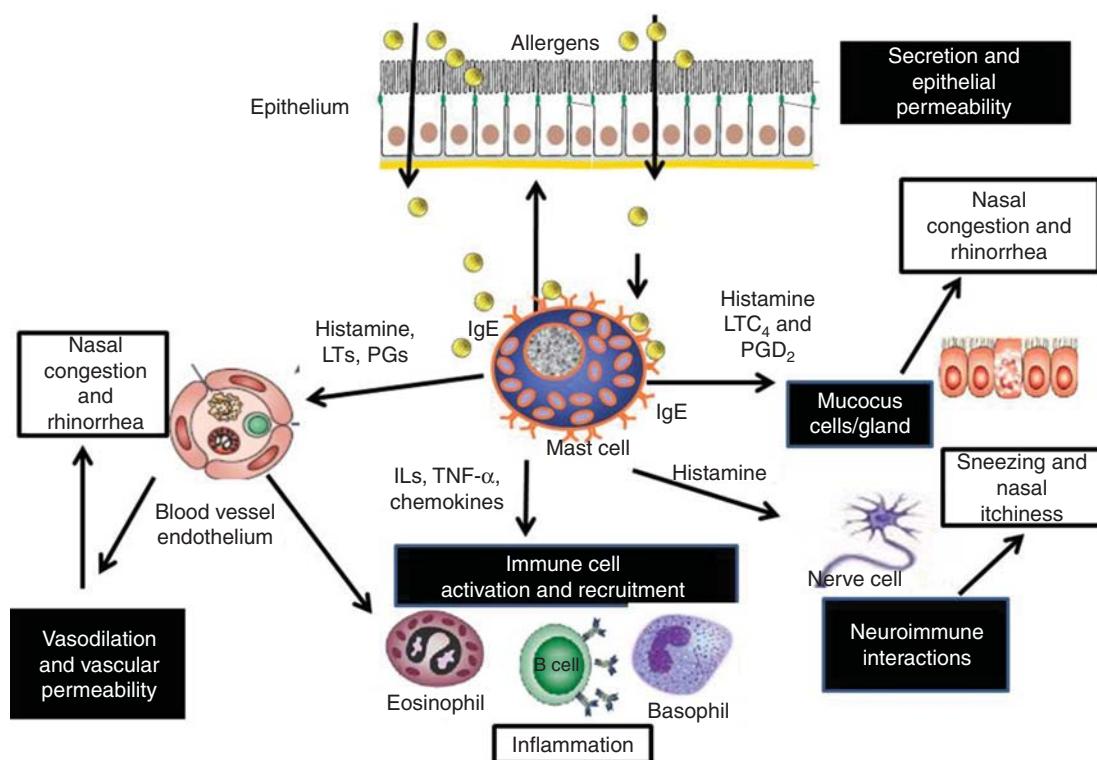


Figure 1. Pathophysiology of allergic rhinitis. Allergic rhinitis is an IgE mediated disease. Antigen-specific IgE binds to high-affinity receptors (FcεRI) on tissue mast cells, basophils and dendritic cells. The early phase response mediators cause the characteristic symptoms of AR-watery rhinorrhea, sneezing and itching-within minutes of allergen exposure. This is followed by the late phase response, involving the infiltration of inflammatory cells due to cytokine and chemokine release resulting in congestion and inflammation.

capsaicin desensitization and surgery for complications like nasal polyps/deviated nasal septum [12].

2.2 New compounds for the treatment of AR

Many different classes of medications are currently under development for allergic respiratory diseases. However, most are being developed for allergic asthma due to the greater morbidity and costs of this disease and the potential for fatalities. The exception is allergen immunotherapy where a variety of novel modalities are being explored for both AR and asthma.

2.3 Introduction to omalizumab

Ig E, first described by Ishizaka in 1967 [26], plays a pivotal role in the development of allergic inflammation by binding to receptors on effector cells and triggering the release of inflammatory mediators [8,12]. Omalizumab (Xolair®) is a monoclonal antibody directed against the high-affinity receptor binding domain of IgE (Box 1). Omalizumab has been developed for the treatment of allergic asthma and is approved by FDA for moderate to severe chronic persistent allergic asthma. Its role in the management of AR has been evaluated

in a number of trials. The aim of this review is to evaluate and clarify the role of omalizumab in the treatment of AR.

2.4 Chemistry, pharmacodynamics and pharmacokinetics

2.4.1 Chemistry

Omalizumab is a humanized, monoclonal antibody that recognizes and binds to the Fc portion of the IgE molecule (Table 1) [27]. Approximately 5% of omalizumab is composed of murine sequences which were engrafted onto a human IgG1κ framework; it is these portions that contain the antigen (IgE) binding regions of the molecule (Figure 3: omalizumab structure) [28,29]. Omalizumab binds to the Cε3 domain of the IgE molecule, which is conserved among all IgE molecules [30]. This is the same site by which IgE binds to FcεRI. The binding of omalizumab to IgE results in the formation of soluble immune complexes that are subsequently cleared by the reticuloendothelial system. Typically, omalizumab forms trimers of two omalizumab molecules per IgE antibody but can form other complexes (Figure 4: omalizumab IgE complexes) [31]. In essence, binding of omalizumab to free IgE prevents the binding of IgE to FcεRI and the subsequent expression of IgE on the surface of allergic effector cells. As

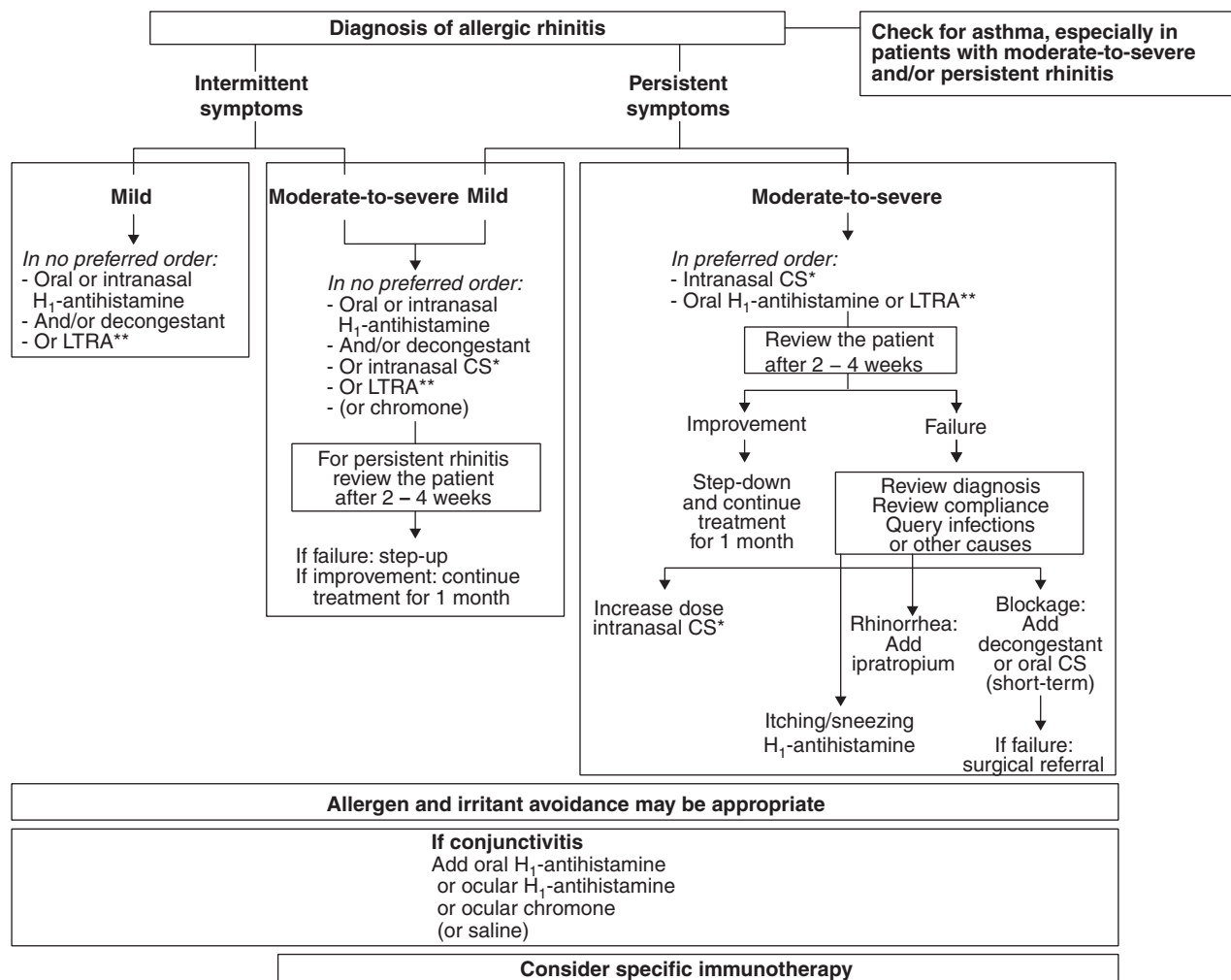


Figure 2. Treatment paradigm of allergic rhinitis. Step wise treatment of allergic rhinitis based on the severity of symptoms.

omalizumab binds to the same site that IgE molecules use to attach to FcεRI, it cannot cross-link surface expressed IgE; hence, it cannot precipitate degranulation of effector cells [28]. However, omalizumab has been reported to cause anaphylaxis by as yet to be determined mechanisms.

2.4.2 Pharmacodynamics

2.4.2.1 Mechanism of action: (Figures 4 and 5)

The primary mechanism of action of Omalizumab is the binding of free IgE in the circulation (Figure 5). Together, they form small biologically inert complexes, usually trimers, which are cleared by the reticuloendothelial system [30,32].

The secondary mechanism of action is by reduction of FcεRI receptors and possibly the low-affinity IgE receptor CD23. In human studies, omalizumab resulted in a dramatic reduction in the number of FcεRI receptors on basophils [33-35]. The functional consequence of the FcεRI down regulation was a 90% decrease in histamine release from the basophils in response to *ex vivo* challenge with house dust mite [34]. Omalizumab also causes rapid reduction in expression of dendritic

cell and mast cell FcεRI [27,36,37]. It also has additional effects like decreasing eosinophils, T and B-lymphocytes and other inflammatory cells from respiratory tissue [38-41].

2.4.2.2 Effects on serum IgE levels

Serum free IgE levels are rapidly suppressed in a dose-dependent manner following intravenous or subcutaneous administration of omalizumab and correlate with improvements in clinical outcome [42,43]. The formation of omalizumab-IgE complexes resulted in a significant two- to ninefold dose dependent increase in total IgE levels due to formation of complexes (free IgE levels decreased) [31,44-46].

2.4.3 Pharmacokinetics

The serum omalizumab concentration following subcutaneous or intravenous administration of single or multiple doses was described by a 2-compartment model with a volume of distribution approximating plasma volume [47]. The pharmacokinetic profile of omalizumab was similar in adults, adolescents and children [28].

Table 1. Features and properties of omalizumab (rhuMAB-E2525).

<i>Indications</i>	
Allergic asthma	
Allergic rhinitis (not FDA approved)	
<i>Mechanism of action</i>	
Recombinant monoclonal humanized anti-IgE Antibody	
Binds to Fc portion of IgE, blocking binding of mast cell receptor FcεRI	
<i>Dosage and administration in clinical trials</i>	
Allergic asthma	150 – 300 mg every 4 weeks or 225 – 375 mg every 2 weeks dependent on bodyweight and baseline IgE
Allergic rhinitis	300 mg every 4 week dependent on baseline IgE
Route of administration	Subcutaneous
<i>Pharmacokinetic profile</i>	
Peak plasma concentration (dosage)	30.9 mg/L (1 mg/kg IV)
Time to peak plasma concentration	≤ 14 days (0.15 mg/kg SC)
Volume of distribution	Approximating plasma volume
Elimination half-life	1 – 4 weeks
<i>Adverse events</i>	
Drug-related	Mild urticaria

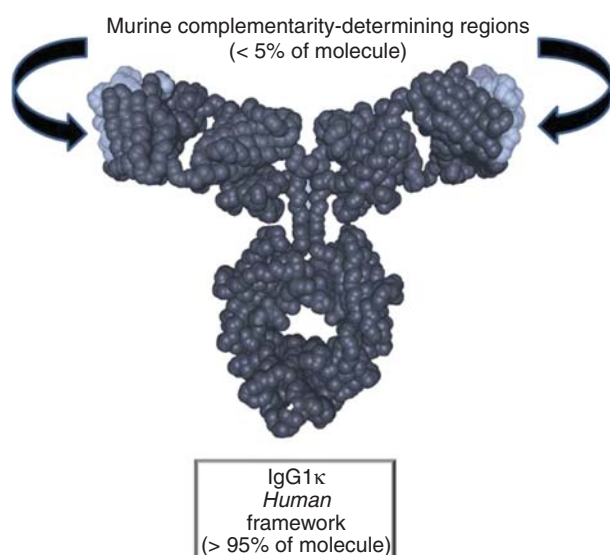


Figure 3. Structure of omalizumab. Omalizumab is a humanized monoclonal antibody; 5% of omalizumab is composed of murine sequences which were engrafted onto a human IgG1κ framework; omalizumab binds to the Cε3 domain of the IgE molecule, which is conserved among all IgE molecules.

2.4.3.1 Dosing

The only FDA approved anti-IgE therapy is omalizumab (Xolair®). This is supplied as lyophilized powder, 150 – 175 mg on reconstitution with sterile water for subcutaneous injection. The recommended dose for allergic asthma is 0.016 mg per kg of body weight per international unit/mL of IgE for every 4 weeks, administered subcutaneously at either 2- or 4-week intervals for adults and adolescents [44,48].

Currently the only FDA approved indication is moderate to severe perennial allergic asthma. Dosing charts are used to calculate the correct dose [44,49].

The peak serum concentration of > 2 mg/L is reached by 14 days after subcutaneous administration of omalizumab 0.15 mg/kg [42]. Omalizumab was cleared slowly from circulation with a terminal elimination half-life of 1 – 4 weeks [42,47].

2.5 Clinical efficacy in AR (Table 2)

There have been many studies on the use of omalizumab in AR (Table 1). It has been proven to have multiple beneficial effects in patients with AR such as decreasing daily symptoms and rescue medication usage as well as decreasing nasal allergen challenge responses. It helped in improving quality of life and decreased missed school or work days [50,51].

In a large study, the effect of omalizumab was evaluated in 536 patients with ragweed-sensitive AR [52]. Patients were randomized to receive one of three omalizumab doses (50 mg, 150 mg, or 300 mg) or placebo. Omalizumab or placebo was administered just prior to the onset of the ragweed season and every 3 – 4 weeks throughout the pollen season. Subjects treated with 300 mg omalizumab demonstrated significantly lower nasal symptom scores; improved rhinitis quality of life scores (RQLQ), and less days missed from work or school when compared with placebo. In addition, a significant correlation was observed between reduction in serum IgE and improvements in nasal symptoms and rescue antihistamine use.

Another large seasonal AR study examined the therapeutic benefits of omalizumab in 251 birch-pollen sensitive patients [43]. Subjects received 300 mg omalizumab or placebo two or three times during the birch pollen season dependent on their baseline total serum IgE values. The omalizumab-treated group showed significant improvements over placebo in average daily symptom scores, usage of rescue antihistamines, and quality of life measures.

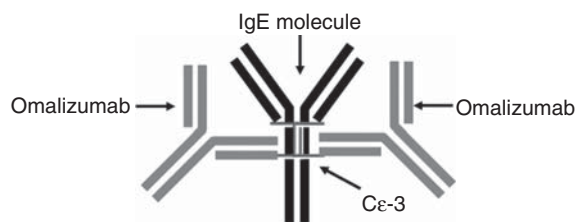


Figure 4. IgE and omalizumab immune complexes. The binding of omalizumab to IgE results in the formation of soluble immune complexes; typically, omalizumab forms trimers of two omalizumab molecules per IgE antibody.

In patients with ragweed-induced AR, omalizumab has been safely re-administered in a subsequent year after discontinuation following the previous ragweed season [53].

Omalizumab has also been shown to be effective in the treatment of perennial AR. A total of 289 patients with moderate-to-severe disease were evaluated in a 16-week trial. Patients were randomized to omalizumab (0.016 mg/kg/IgE [IU/mL]) or placebo for every 4 weeks [54]. Both mean daily nasal symptom severity scores and rescue antihistamine use were significantly lower in the omalizumab group when compared with placebo ($p < 0.001$ and $p \leq 0.005$, respectively).

The effect of omalizumab on early nasal responses to allergen challenge was investigated in two randomized, double-blind, placebo-controlled trials involving patients with AR [55,56]. Both studies showed significant inhibition of allergen-induced acute nasal responses, with inhibitory effects apparent within 2 weeks of treatment. Furthermore, the inhibition of nasal responses correlated temporally with the reduction in FcεRI on basophils, suggesting that inhibition of allergic responses by omalizumab requires reduction in FcεRI expression as well as serum IgE levels [55]. A significant decrease in basal TNF- α and albumin in the nasal lavage fluid (a marker of vascular permeability) was also shown in omalizumab-treated patients [56].

The efficacy of omalizumab in the treatment of Japanese cedar pollen-induced seasonal AR has been demonstrated in multiple Japanese studies [57-60]. A randomized, double-blind, placebo controlled, multicenter study done on 100 patients showed that omalizumab administered every 2 – 4 weeks was effective in the treatment of SAR induced by Japanese cedar pollen [59]. Another open-label study [58] demonstrated the safety and efficacy of omalizumab when it was re-administered in the second Japanese cedar-pollen season. A large randomized, double-blind, double dummy study [57] done on 308 patients showed that omalizumab is more effective than supatast tosilate in the treatment of Japanese cedar pollen-induced seasonal AR.

2.5.1 Role of omalizumab in patients with AR and asthma

AR and asthma frequently coexist. Poor control of rhinitis may exert a detrimental effect on asthma. The SOLAR study

evaluated 405 patients, adolescents and adults, with moderate-to-severe asthma on stable therapy who also had persistent AR [61]. Patients received omalizumab or placebo for 28 weeks. Fewer asthma exacerbations were observed in the omalizumab-treated patients than placebo-treated patients (20.6 vs. 30.1%). Furthermore, more patients in the omalizumab group demonstrated a clinically significant improvement in both asthma and rhinitis quality of life indices (57.7 vs. 40.6%). This suggests omalizumab is effective in the treatment of upper and lower airway symptoms in the same patients.

2.5.2 Using omalizumab with immunotherapy

The rationale for using the combination of anti-IgE and allergen immunotherapy comes from pre-existing data about the biologic and immunologic effects of both therapies. Allergen immunotherapy has been used for 100 years for the management of allergic disorders and is the only antigen-specific immunomodulatory treatment routinely available to clinicians. However, immunotherapy is associated with the risk of allergic reactions to the allergens used.

Omalizumab does not completely ameliorate symptoms of allergic respiratory symptoms, and on discontinuation, serum IgE levels return to pre-treatment levels [43,50,52]. There are no data concerning long lasting immune tolerance as a result of anti-IgE therapy. Nonetheless, omalizumab-induced decreases in serum IgE and the expression of FcεRI on key immune effector cells, including basophils and dendritic cells could lead to important immunologic changes that could enhance the immune tolerance to allergens delivered by immunotherapy [34,36,55]. Thus, combining omalizumab plus allergen immunotherapy improves the prospects of better clinical benefits and safety.

The addition of omalizumab to standard maintenance dose immunotherapy was evaluated in 221 children and adolescents with sensitization to birch and grass allergen [62]. During birch season, both birch and grass immunotherapy plus omalizumab groups had decreased symptoms, by 39% in the group treated with irrelevant immunotherapy (grass) and by 48% in the birch immunotherapy group compared to irrelevant immunotherapy and placebo. Similar results were seen in grass season with irrelevant (birch) immunotherapy and omalizumab decreasing symptoms by 45% while patients on grass immunotherapy and omalizumab had a reduction in symptom scores by 71% compared to irrelevant immunotherapy and placebo. When these findings were further analyzed for the grass pollen allergic children it was noted that omalizumab plus immunotherapy treated groups had significantly diminished rescue medication usage and number of symptomatic days when compared to either omalizumab or immunotherapy alone [63]. The combined treatment with both omalizumab and grass immunotherapy was more effective than omalizumab alone.

The primary objective of another study was to determine whether omalizumab, given 9 weeks prior to rush immunotherapy, followed by 12 weeks of dual omalizumab and

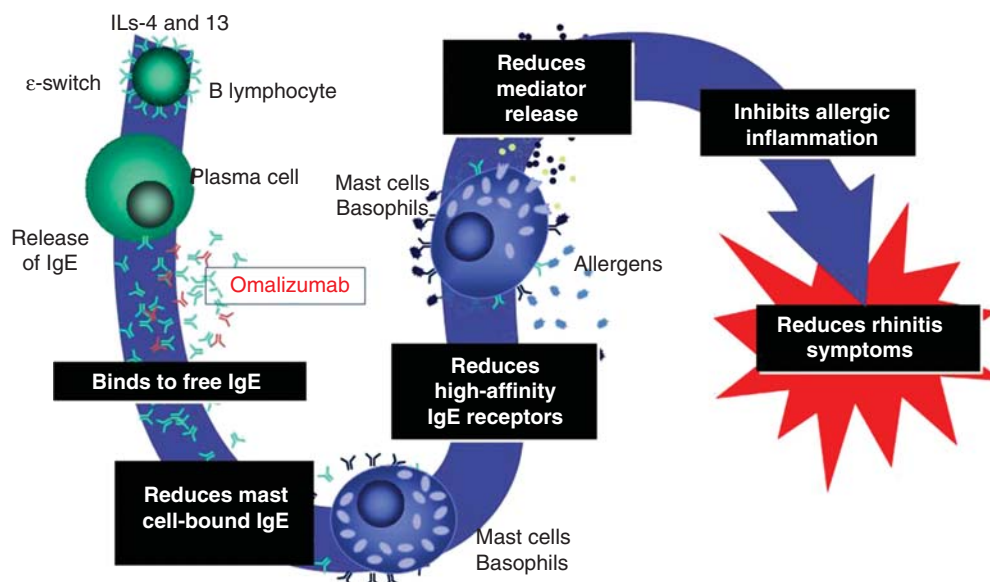


Figure 5. Mechanism of action of omalizumab. Primary mechanism of action of omalizumab is the binding of free IgE in the circulation resulting in small biologically inert complexes which are cleared by the reticuloendothelial system. A key secondary mechanism of action is reduction of FcεRI receptors on basophils and mast cells.

immunotherapy, is more effective than rush immunotherapy followed by immunotherapy alone in ragweed allergic patients [64]. A major secondary objective was whether omalizumab improved the safety of rush immunotherapy. Omalizumab improved both the efficacy and safety of immunotherapy. Patients receiving omalizumab plus immunotherapy had fewer adverse events than those receiving immunotherapy alone. *Post-hoc* analysis of groups receiving immunotherapy demonstrated that the addition of omalizumab resulted in a fivefold decrease in risk of anaphylaxis caused by rush immunotherapy (odds ratio, 0.17; $p = 0.026$). On an intent-to-treat basis, patients receiving both omalizumab and immunotherapy showed a significant improvement in severity scores during the ragweed season compared with those receiving immunotherapy alone (0.69 vs. 0.86; $p = 0.044$). Thus, combined therapy with omalizumab and allergen immunotherapy may be an effective strategy to permit more rapid and higher doses of aeroallergen immunotherapy to be given more safely and with greater efficacy to patients with allergic diseases [64].

2.6 Safety and tolerability

Omalizumab has proven to be a generally well-tolerated medication with few serious adverse reactions (Table 3). The most common adverse event is a local reaction at the injection site that may include burning, pruritus, hives, pain, redness, induration, swelling, warmth and bruising. Severe local cutaneous reactions occurred in 12% of omalizumab-treated subjects and 9% of placebo-treated subjects [49].

Other frequent adverse events in patients treated with omalizumab were: viral infections (23%), sinusitis (16%),

headaches (15%) and pharyngitis (11%). These events occurred at similar rates in omalizumab-treated patients and placebo-treated patients [49]. Only 6.6% of the total adverse events were felt to be treatment-related in the omalizumab group versus 5.6% in the placebo group.

The safety of omalizumab was evaluated in > 300 children in a randomized, double-blind, placebo-controlled study [65]. Subjects were treated for 28 weeks followed by a 24-week open label extension. During the double-blind 28-week treatment period, the incidence rate of adverse events was similar between omalizumab and placebo. Urticaria was reported in eleven patients (4.9%). With the exception of one severe case of urticaria that necessitated withdrawal from the study, all patients with urticaria had either spontaneous remission or resolution with antihistamine treatment. Adverse event incidence during the open label extension was similar to the omalizumab-treated group during the 28-week double-blind phase. The results of this study suggested that omalizumab is well tolerated in children and has a good safety profile.

In the original studies, there were 4127 patients who received omalizumab, and of these, 19 or 0.46% developed cancer. A total of 2236 patients received placebo treatment and 5 or 0.22% of this group developed cancer [49]. Of 3726 patients who received omalizumab in controlled clinical trials only 0.35% developed cancer. None of the differences between these groups were statistically significant. All tumors, but one (a recurrent non-Hodgkin's lymphoma) were solid tumors. Thus, it is very likely that most of these tumors were pre-existent. Indeed, a history of cancer was not an exclusion criterion if greater than 3 months prior to enrollment in the initial studies. Overall, the conclusion of an

Table 2. Studies of omalizumab use in allergic rhinitis.

Type of study	Authors	Refs.	Treatments	N/allergen	Conclusions
Randomized, double-blind, Placebo-controlled, multicenter	Casale <i>et al.</i>	[42]	Initial intravenous loading dose followed by administration of rhuMAB-E25 subcutaneously A subcutaneous placebo group and an intravenous placebo group	240/ragweed	Decreased serum free IgE in a dose-dependent fashion; an effective therapy for ragweed induced allergic rhinitis in those patients achieving significant reductions in free IgE
Randomized, double-blind, Placebo-controlled, multicenter	Casale <i>et al.</i>	[52]	Randomly assigned to receive omalizumab subcutaneously just prior to ragweed season and repeated during the pollen season	536/ragweed	Omalizumab decreased serum free IgE levels and provided clinical benefit in a dose-dependent fashion in patients with seasonal allergic rhinitis due to ragweed
Randomized, double-blind, Placebo-controlled, multicenter	Alderoth <i>et al.</i>	[43]	Randomly, receive 300 mg of rhuMAB-E25 or placebo given 2 or 3 times during the birch pollen season, depending on baseline IgE levels	251/birch-pollen	Compared with placebo, rhuMAB-E25 was safe and effective in controlling birch pollen-induced SAR symptoms, with less concomitant medication use and improved QOL
Randomized, double-blind, Placebo-controlled, multicenter	Chervinsky <i>et al.</i>	[54]	Randomized to 16 weeks' double-blind subcutaneous treatment with either placebo or omalizumab	289/perennial allergic rhinitis	Omalizumab was safe and well tolerated in the treatment of patients with PAR, providing effective control of symptoms and improved RQoL while simultaneously minimizing reliance on rescue antihistamines
Randomized, double-blind, Placebo-controlled, multicenter	Nayak <i>et al.</i>	[53]	Safety and tolerability of retreatment with omalizumab in 287 patients previously treated with this agent	287/ragweed	Retreatment during second pollen season with omalizumab, 300 mg every 3 or 4 weeks, was well tolerated and was not associated with any significant adverse/immunologic reactions
Randomized, double-blind, Placebo-controlled, multicenter	Okubo <i>et al.</i>	[59]	Omalizumab or placebo was administered subcutaneously every 2 or 4 weeks based on serum total IgE and body weight at baseline	100/Japanese cedar	Omalizumab was effective and safe in the treatment of SAR induced by Japanese cedar pollen
Open-label	Ogino <i>et al.</i>	[58]	Omalizumab was administered subcutaneously every 2 or 4 weeks based on the serum IgE level and body weight of each patient	34/Japanese cedar	Omalizumab was effective and safe when consecutively readministered in the second Japanese cedar pollen season
Randomized, double-blind, Double-dummy, multicenter	Nagakura <i>et al.</i>	[57]	Patients were treated for 12 weeks with omalizumab plus placebo of suplatast tosilate or suplatast tosilate plus placebo of omalizumab	308/Japanese cedar pollen-induced SAR	Omalizumab showed significantly greater improvements than suplatast tosilate in the treatment of SAR induced by Japanese cedar pollens

Table 3. Adverse effects of omalizumab.

<i>Common (> 100 to < 1/10)</i>
Pyrexia
Upper abdominal pain
Headache
Injection site reactions: swelling, erythema, pain, pruritus
<i>Uncommon (> 1/1000 to < 1/100)</i>
Pharyngitis
Syncope, dizziness, paresthesias
Postural hypotension, flushing
Allergic bronchospasm, coughing
Diarrhea, nausea
Urticaria
Influenza like illness
<i>Rare (> 1/10,000 to < 1/1000)</i>
Parasitic infection in endemic areas
Anaphylactic reaction
<i>Frequency unknown, some case reports</i>
Idiopathic severe thrombocytopenia
Serum sickness
Allergic granulomatous vasculitis
Alopecia
Arthralgia and myalgia

independent panel of oncologists when they compared the cancer rates for those reported in this population range was that there was no relative risk, which was statistically significant for treatment with omalizumab. Nonetheless, post-approval surveillance is appropriate. Two recent abstracts evaluated the possible risks of malignancy associated with omalizumab [66,67]. The first compiled data from 32 randomized, double-blind, placebo-controlled studies and assessed for incidence of primary malignancy [66]. Data collection occurred between 1994 and 2010. The primary analysis identified a similar number of primary malignancies in omalizumab-treated (14/4254) and control patients (11/3178), and found no difference in the risk of malignancy in patients exposed to omalizumab compared with controls. An Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate to Severe Asthma (EXCELS) was a multicenter prospective cohort study of approximately 5000 omalizumab and 2500 non-omalizumab-treated patients recruited from a variety of practice settings in the USA [68]. These more recent data suggest that omalizumab might have a better safety profile in regards to malignancy than that suggested by early studies.

In the clinical trials, there was no increase in type I hypersensitivity adverse events with an overall incidence of urticaria of 1.2% (39/3224) in the omalizumab group and 1.1% (24/2019) in control patients. There are rare cases of acute systemic allergic reactions occurring after omalizumab treatment. These events occurred after the first and multiple doses and often did not manifest until at least 60 min post injection. The mechanisms are unclear [69]. Even though the mechanism is unknown, patients can be successfully desensitized to omalizumab and continue on therapy [70]. In an 18-month period, 2007 – 2008, 118 cases of anaphylaxis or multisystem allergic

reactions were reported [71]. There is no evidence of any immune complex disease associated with omalizumab treatment and in 1723 patients studied only one demonstrated anti-omalizumab antibodies.

One potential concern with decreasing serum IgE would be the potential for increased incidence or severity of helminthic infections. A 1-year clinical trial in Brazil was performed with 68 patients treated with omalizumab and 69 placebo controls [72]. When adjusted for study visit, baseline infection status, gender and age the odds ratio for helminth infection was 2.2 (95% C.I.: 0.94, 5.15) indicating a patient who had infection was anywhere from 0.94 to 5.15 times as likely to have received omalizumab as a patient who did not have an infection. Response to anti-helminth therapy was not different between treatment groups. Patients at high risk of helminthic infection should be monitored for infection while on omalizumab therapy.

Post-marketing reports of possible side effects have arisen since omalizumab was approved. One case of severe thrombocytopenia was noted. Thrombocytopenia has been added to potential adverse events associated with omalizumab even though no causal relationship was established, and routine platelet monitoring is not required. In addition, rare cases of alopecia have been reported (< 0.1%), but no causal relationship to omalizumab has been established [49].

In response to the data on anaphylaxis and anaphylactoid reactions to omalizumab the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma and Immunology appointed a task force to review the data between June 1, 2003 and December 31, 2005 [73]. A subsequent follow-up report was published in 2011 after review of data from January 1, 2006 to December 31, 2008 [74]. These two reports make several recommendations for the administration of omalizumab as seen in Table 4.

2.7 Regulatory and financial affairs

Currently, omalizumab is FDA approved only for moderate-to-severe persistent asthma patients who are 12 years or older, have IgE levels of greater than or equal to 30 IU/mL and less than or equal to 700 IU/mL and their symptoms are inadequately controlled with the maximum dose of inhaled corticosteroids and/or a long-acting β_2 [49].

The effectiveness and safety of omalizumab in the treatment of AR have been demonstrated by multiple studies [42,43,50-54,59]. Omalizumab cost is high, ranging from \$6,000 to \$24,000 a year [49]. However, AR is a chronic respiratory illness and has a substantial financial burden [3,4,22,23].

Recent studies in asthma [75,76] have shown that additional cost due to the use of omalizumab was offset by the medium- and long-term savings associated with the reduction in hospital admissions and emergency department visits. Omalizumab added to an optimized therapy significantly improves clinical outcomes in difficult-to-treat, persistent allergic asthma. Costs also increased, but proved justified by health benefits achieved.

Table 4. Recommendations for omalizumab administration [73,74].

Informed consent should be obtained after discussing risks and benefits
The patient should be educated on signs, symptoms and treatment for anaphylaxis
Patients should be prescribed and educated on the proper use of an epinephrine auto injector and advised to carry this before omalizumab administration and for the next 24 h
Assess patient's current health prior to administration including vital signs and some measure of pulmonary function
Patients should be observed for 2 h after the first three injections of omalizumab. Subsequent injections require observation for 30 min, but wait period can be modified based on a physician's clinical judgment

For patients, with severe refractory AR, anti-IgE treatments might have the potential of reducing their financial burden both in terms of medical costs and loss of productivity in missed work and school days. There are no studies available about the cost-effectiveness of omalizumab in AR. However, AR and asthma are often seen together and control of AR helps prevent acute exacerbations of asthma [6,7,22,77,78].

Hence, it is reasonable to say that use of omalizumab will help to improve the morbidity of AR; although there will be an increase in the direct cost of treatment. However, some of the extra costs could be offset by improvement in quality of life, decrease in work and school hours lost, and decrease in indirect and total cost of management of AR.

3. Conclusion

The development of a selective anti-IgE humanized monoclonal antibody represented a novel and important therapeutic option for severe asthma and other allergic diseases. The data suggest omalizumab inhibits activation of mast cells and basophils and decreases the effects of other inflammatory cells such as eosinophils through a variety of mechanisms. This has resulted in clinical improvements in patients with moderate-to-severe allergic asthma, including significant reductions in exacerbations.

To summarize, the primary benefits of omalizumab for asthma are multifold. It causes decrease in exacerbations, modestly improved lung function, and reduced numbers of emergency visits to the doctors. Some patients responding to omalizumab can reduce or spare entirely the use of inhaled and/ or oral corticosteroids, which cause multiple serious side effects, when used at high doses for extended periods. As the free IgE in patients is depleted by omalizumab, the FcεRI receptors on basophils, mast cells and dendritic cells are gradually down-regulated and render these cells much less sensitive to stimulation by allergens.

Omalizumab appears to be a relatively safe, well-tolerated medication. There are a few limitations of omalizumab use. It is used primarily in patients with severe, persistent allergic asthma, uncontrollable with oral and/or high-dose inhaled

corticosteroids usually on concomitant long-acting β-agonists. Its use in AR has been limited due to its high cost, non-regulatory approval for this indication and its injectable dosage form requiring administration every 2 – 4 weeks.

Several studies have been done on the role of omalizumab in treatment of AR, and they have indicated success with improvement in quality of life and decrease in the use of rescue medications. Although, not FDA approved, it appears to be a promising agent for the treatment of severe cases of AR, especially seasonal rhinitis. We postulate that it can be prescribed just before the peak allergy season and can prevent the morbidity from acute SAR.

Hence, it is reasonable to conclude that omalizumab could reduce the morbidity of AR; although, there will be an increase in the direct cost of treatment. However, it could partially be offset by improvement in quality of life, decrease in work and school hours lost, and decrease in indirect and total cost of management of AR.

4. Expert opinion

Omalizumab is a humanized antibody to IgE, and is licensed for use in moderate to severe asthma. Several studies have confirmed that it is an efficacious agent, with a good safety profile.

A lot of work has been done by different investigators to show its efficacy in treatment of AR, both seasonal and perennial. It has also been extensively proven that AR and asthma are often co-existent and control of rhinitis symptoms helps in preventing the morbidity of asthma as well as emergency visits and hospitalizations.

Omalizumab has also proven that its concomitant use with immunotherapy makes it more efficacious and safer for both AR and asthma.

The high cost of omalizumab is definitely an obstacle for the more frequent prescribing of this effective medication; however, that can be partially offset if we compare the direct costs of treatment with the overall financial burden of AR. Further studies need to be done to elucidate and highlight this.

We suggest that the pre- and co-season use of omalizumab could be an effective strategy for preventing acute flare up of SAR and may prove more cost-effective in this setting. Its use in PAR is more controversial, as although it has been shown to be effective clinically, it would have to be dosed throughout the year making it unlikely to be cost-effective.

Finally, omalizumab has proved to be very valuable in helping to understand the importance of IgE in the pathogenesis of both AR and asthma.

Declaration of interest

Vashisht has no relevant conflict of interest and neither author received payment for the preparation of this manuscript. Casale has been a principal investigator on studies using omalizumab funded to Creighton University, and he has served on advisory boards for both Genentech and Novartis.

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