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Targeting the IgE molecule in allergic and asthmatic diseases: Review of the IgE molecule and clinical efficacy

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Introduction	S376
IgE molecule	S376
Regulation of IgE synthesis	S377
FcεRI	S377
FcεRI activation	S377
Regulation of FcεRI expression	S378
FcεRII (or CD23)	S378
IgE in antigen-presenting cells	S378
Monoclonal anti-IgE molecule	S378
Omalizumab: Clinical application	S379
Clinical studies: Allergic asthma	S379
Clinical studies: Allergic rhinitis	S381
Clinical studies: Food allergy	S382
Clinical dosing	S382
Adverse events and safety	S383
Conclusions	S383

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Targeting the IgE molecule in allergic and asthmatic diseases: Review of the IgE molecule and clinical efficacy

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Diseases such as allergic asthma and rhinitis continue to increase in the United States, affecting millions of persons.¹ It is well established that allergy contributes to the pathogenesis of most asthma, especially in children and young adults.² Despite current therapy (eg, inhaled corticosteroids, antileukotrienes, and bronchodilators), patients with moderate-to-severe asthma continue to remain symptomatic and experience frequent exacerbations of disease requiring oral corticosteroids, emergency department treatments, and hospitalizations.

Allergic diseases are traditionally referred to as immediate or type 1 hypersensitivity reactions, with IgE as a critical factor. IgE is involved in allergic inflammation, especially in the early-phase response, but it might also be involved in the late-phase allergic response. A direct correlation between serum IgE levels and asthma exists.^{2,3} As log IgE values increase, asthma prevalence increases linearly, even in patients who are categorized as having nonallergic asthma.² In addition, there is a significant, although lower, association in allergic rhinitis with IgE levels and positive skin test reactivity to pollens.²

Recent advances in our understanding of the role of IgE in allergic inflammation have led to the development of an mAb to IgE that reduces IgE levels, thereby reducing allergic inflammation. This review aims to provide an overview of the basic science of the IgE molecule and the

Abbreviations used

AID: Activation-induced cytidine deaminase
APC: Antigen-presenting cell
DC: Dendritic cell
ICS: Inhaled corticosteroid
SIT: Specific immunotherapy

clinical efficacy of anti-IgE therapy in allergic and asthmatic diseases.

IgE MOLECULE

In 1967, Ishizaka and Ishizaka⁴ described a new antibody isotype, the IgE molecule. Since its discovery, IgE has been shown to be important in allergic diseases, as well as in immune responses to parasitic infection.⁵⁻⁷ The IgE molecule is composed of 2 light chains and 2 heavy chains. The overall structure is similar to other classes of antibodies, but it is distinguished by the sequence of the ϵ -heavy chain constant region. As opposed to IgG, which contains 3 heavy chains, IgE contains 4 heavy chain constant domains (C ϵ 1-C ϵ 4).⁸ The additional domain (C ϵ 2) replaces the hinge region.⁹

The allergen-binding site is located on the variable regions of the heavy and light chains. The Fc fragment of the IgE molecule is able to bind to 2 types of immunoglobulin Fc receptors, the high-affinity IgE receptor (Fc ϵ RI) and the low-affinity IgE receptor (Fc ϵ R2 or CD23). The binding site for both the Fc ϵ RI and Fc ϵ R2 is located in proximity to but on different parts of the C ϵ 3 domain of the IgE molecule.^{8,10-12} IgE molecules are mainly produced by plasma cells in the mucosa-associated lymphoid tissue.¹³ Most of the IgE that is produced is bound by Fc ϵ RI expressed by mast cells and basophils.¹³ In nonallergic individuals the level of plasma IgE is 10,000- to 50,000-fold less than that of plasma IgG. Even in highly atopic individuals, the level of plasma IgE remains less than 1000-fold that of plasma IgG.¹³

The dimeric Fc fragment of the IgE antibody has full binding activity for Fc ϵ RI.¹⁴⁻¹⁶ IgE antibody binds to Fc ϵ RI in the absence of antigen, and thus the receptor

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adopts the antigenic specificity of the prevalent IgE repertoire.⁸ Cross-linking of the receptor through antigen-antibody interaction leads to the initiation of a signal transduction cascade and downstream effects.¹⁷

Regulation of IgE synthesis

The major regulatory step in IgE synthesis is the regulation of IgE class-switch recombination. A comprehensive review of this subject has recently been done.¹³ Common for all isotype switching are the germline transcription of CH genes and the induction of activation-induced cytidine deaminase (AID) expression.¹³⁻¹⁸ IgE class-switch recombination is accomplished through 2 pathways, the classical and alternative pathways.¹³ The classical or T cell-dependent pathway of IgE synthesis involves the presence of IL-4, IL-13, or both during ligation of the CD40-CD40 ligand (CD154) that leads to the induction of C ϵ germline transcription and induction of AID.

In contrast, the alternative pathway does not require T-cell interaction but does require the presence of IL-4. For example, corticosteroids can induce IgE synthesis in the presence of IL-4 by upregulating CD40 ligand expression on T and B cells.^{19,20} A second pathway to induce class switching to IgE exists when B cell-activating factor belonging to the TNF family and a proliferation-inducing ligand expressed on monocytes and dendritic cells (DCs) bind to their respective receptors on B cells in the presence of IL-4.²¹ In addition, EBV can nonspecifically induce IgE class switching, which is likely due to CD40 mimicry by virus-encoded latent membrane protein 1.^{13,22} A regulatory protein in the classical complement pathway, C4 binding protein has been shown to mimic the CD40 ligand.²³ In the presence of IL-4, the interaction between this molecule and CD40 will induce transcription of germline C ϵ and expression of AID, thereby causing class switch to IgE.^{13,23}

IgE class switching is negatively regulated by several mechanisms. Cytokines, such as IFN- γ and IL-21, inhibit IgE class switching, perhaps because of inhibition of the development of T_H2 cells, the suppression of C ϵ germline transcription, or both.¹³ Various B-cell surface receptors (B-cell receptor, CD45, CTLA4, and CD23) inhibit IgE class switching through different mechanisms, such as altering the signal transduction cascade that leads to IgE class-switch recombination.¹³ Several transcription factors, such as B-cell lymphoma 6 and inhibitor of DNA binding 2, can also inhibit IgE class switching. B-cell lymphoma 6 competitively inhibits signal transducer and activator of transcription 6 binding, thus repressing IL-4-induced C ϵ germline transcripts.²⁴ Inhibitor of DNA binding 2 can also block C ϵ germline transcripts by skewing the cytokine profile to a T_H1-type cytokine profile.²⁵

FC ϵ RI

FC ϵ RI belongs to an antigen receptor superfamily that includes the B-cell receptor, T-cell receptor, and several

IgG Fc receptor isotypes.⁸ As the name implies, the high-affinity IgE receptor binds with a high affinity to the IgE molecule, with an equilibrium dissociation constant or binding affinity of 10^{-9} to 10^{-10} M.⁸ Fc ϵ RI consists of 4 transmembrane polypeptides with the composition $\alpha\beta\gamma 2$.⁹ This tetramer structure is only expressed on mast cells and basophils. An alternate form, an $\alpha\gamma 2$ trimer,¹⁷ is expressed on a variety of other hematopoietic cell lines, including eosinophils,²⁶ DCs, activated macrophages, and Langerhans cells.²⁷⁻³⁰

The extracellular portion of the α chain binds to the C ϵ 3 of the IgE molecule.^{8,17} The β and γ chains are required for receptor transmembrane insertion and intracellular signal transduction.¹⁷ Although the α subunit is highly N-glycosylated, glycosylation is not necessary for IgE binding.³¹ The extracellular region of the α chain contains 2 immunoglobulin domains (D1 and D2).¹⁷ The crystal structure of the Fc fragment of human IgE bound to Fc ϵ RI α is known.⁸ The 2 immunoglobulin domains of Fc γ RI α are positioned at an acute angle to one another, forming a convex surface at the top of the molecule, and a marked cleft is enclosed by the 2 globular immunoglobulin domains.¹⁷ Through the discovery of the crystal structure, it was revealed that one receptor binds one dimeric IgE-Fc molecule asymmetrically through interactions at 2 sites.³² This is important because the interaction of one receptor with the IgE-Fc blocks the binding of a second receptor.¹⁷

Two interaction sites exist for the IgE-Fc on the receptor surface, which explains how a 1:1 complex between antibody and receptor is formed.^{8,33} The 2 C ϵ 3 domains bind asymmetrically to distinct sites on the receptor: one is formed by the C-C' loop in the receptor D2 domain, and the second is involved in the 4 solvent-exposed tryptophans (D1-D2 interface).^{8,17}

Fc ϵ RI activation

Cross-linking of Fc ϵ RI with a multivalent antigen is critical in triggering cellular events, which include the release of mediators (histamine, newly synthesized leukotrienes, and IL-4).^{8,13,17} Whereas other receptor types (hormone or cytokine receptors) dimerize and signal after binding a well-defined ligand, these Fc receptor types act as adaptors between highly variable antigen-binding sites and the intracellular signal transduction machinery.⁸ Flexible linkers between the antibody Fab and Fc arms appear necessary to accommodate the variable structures of Fab-antigen complexes and the need to cross-link 2 or more receptors to initiate signaling.^{8,17,34,35} Therefore multivalent antigens can promote colocalization of receptors but cannot form specific contacts that dimerize FcRs.⁸ However, it remains unclear whether colocalization leads to a specific signaling structure or simply to membrane relocation of the complex.⁸

The Fc ϵ RI α chains do not aggregate in the absence of antigen, probably because of extensive glycosylation.¹⁷ This glycosylation at the surfaces of the α chain prevents premature aggregation and permits interaction with the synthetic machinery.^{17,36} However, binding of multiva-

lent antigen overcomes the intrinsic resistance of the α chains to interaction.¹⁷

Activation of the trimeric Fc ϵ RI on other leukocytes, such as monocytes, might also contribute to the pathogenesis of allergic diseases.³⁷ For example, activation of Fc ϵ RI prevents apoptosis of monocytes by induction of the anti-apoptotic ligands Bcl-2 and Bcl-xL and also protects from CD95 Fas-mediated apoptosis.³⁷ In addition, IL-10 production occurs after cross-linking Fc ϵ RI on monocytes.³⁸ In monocyte cultures with IL-4 and GM-CSF, cross-linking Fc ϵ RI alters monocyte differentiation toward a macrophage species and away from a DC phenotype.³⁸ Also, activation of Fc ϵ RI in atopic donors with high expression of Fc ϵ RI leads to the downstream activation of the proinflammatory transcription factor nuclear factor κ B.³⁹

Regulation of Fc ϵ RI expression

Early observations predicted that the Fc ϵ RI expression on the surface of mast cells and basophils correlates with IgE concentrations such that a reduction in IgE level is predicted to decrease surface expression of Fc ϵ RI.⁴⁰⁻⁴² This has been found true in clinical trials in which a reduction in serum IgE levels led to a reduction in Fc ϵ RI on circulating basophils.⁴³ IgE is able to upregulate Fc ϵ RI expression by a number of mechanisms. IgE binding stabilizes the receptor at the cell surface, which prevents receptor internalization and degradation. In addition, IgE uses a preformed pool of receptors comprising recycled and recently synthesized receptors.⁴⁴

Fc ϵ RII (or CD23)

CD23 is an intriguing molecule with diverse functions. Although the name implies low-affinity binding, it displays only 1 log difference in binding compared with the high-affinity IgE receptor, with an equilibrium dissociation constant or binding affinity of 10^8 M⁻¹ for IgE-antigen complex and 10^7 M⁻¹ for IgE alone.⁴⁵ Unlike other Fc receptors that are structurally classified in the immunoglobulin-like superfamily, CD23 is a C-type lectin, type 2 transmembrane protein with an intracytoplasmic C terminus.⁴⁵ CD23 binds to the C ϵ 3 domain of IgE, which is close to but differs from the Fc ϵ RI binding site.¹⁰

CD23 is expressed as 2 different forms, CD23a and CD23b. CD23a is expressed constitutively on B cells, and CD23b is found on a number of cells, such as monocytes, eosinophils, DCs, Langerhans cells, and platelets.³⁰ Besides binding to IgE, CD23 is known to bind to other ligands, including CD21 and the adhesion molecules CD11b and CD11c, which helps explain the wide variety of its functions.^{46,47} CD23 might be cleaved by proteases to the soluble CD23 form, which is proinflammatory.⁴⁸

Ligation of IgE to CD23 on B cells leads to an array of functions, including B-cell differentiation, apoptosis, and regulation of IgE synthesis.⁴⁶ In contrast, soluble CD23 can upregulate IgE synthesis through various mechanisms. Soluble CD23 competes with membrane CD23 in

binding to IgE. By preventing IgE-membrane CD23 binding, the inhibitory IgE synthesis signals are turned off, thereby allowing increased production of IgE. In addition, triggering CD21 by binding soluble CD23 increases IL-4-induced IgE production, upregulating C ϵ germline transcripts. However, triggering CD21 alone in the absence of an IL-4 signal does not increase C ϵ germline transcripts.⁴⁹

IgE in antigen-presenting cells

The 2 receptors for IgE, Fc ϵ RI and Fc ϵ RII (or CD23) are expressed on antigen-presenting cells (APCs) and are critical in facilitating allergen presentation to allergen-specific T cells.³⁰ The main role of Fc ϵ RI on APCs is antigen focusing. Multivalent allergens activate Fc ϵ RI-bound IgE on APCs, initiating a cascade of events.³⁰ Fc ϵ RI-bound IgE is internalized and processed efficiently into specialized endosomal MHC class II compartment-like organelles of DCs. Cathepsin S-dependent ligand peptide loading occurs with the newly synthesized MHC class II molecule for the presentation of Fc ϵ RI-targeted agents.³⁰

DCs are potent APCs that play a significant role in promoting T-cell responses to antigens-allergens. Classically, myeloid precursor DCs (pDC1s or CD11c⁺ cells) are high IL-12 producers that induce a T_H1 response, whereas plasmacytoid DCs (pDC2s or CD123⁺ cells) are low IL-12 producers that induce a T_H2 response.^{50,51} However, it is now known that a given DC subset has remarkable plasticity in directing different types of T-cell responses.^{50,52}

With this background, clinical studies have shown evidence that a monoclonal anti-IgE antibody, omalizumab, affects DCs and therefore might be able to modulate T-cell responses. In addition to downregulating Fc ϵ RI expression on basophils,⁴¹ therapy with omalizumab produced a rapid reduction in surface Fc ϵ RI expression of both precursor DCs type 1 and type 2 subsets.⁴³ A decrease or normalization in DC1s in patients treated with omalizumab during a grass pollen season, but not in the birch pollen season, has been shown.⁵³ These findings might be explained by the fact that in the absence of proinflammatory cytokines and mediators, DC1s promote the differentiation of T_H2 cells. Furthermore, DC1s derived from monocytes and cultured with GM-CSF and IL-4 induce both T_H1 and T_H2 differentiation.⁵⁰ Thus decreased omalizumab-induced IL-4 production by mast cells during the pollen season might cause the apparent reduction in the number of myeloid DCs.⁵⁰ Together, these findings imply that anti-IgE therapy might cause immunomodulation of T-cell responses and inhibit IgE-mediated type 1 hypersensitivity.

Monoclonal anti-IgE molecule

The most recent advance in the treatment of allergic diseases is the development of a monoclonal anti-IgE antibody, omalizumab (Xolair; Genentech/Novartis, South San Francisco, Calif, and Tanox, Inc, Houston, Tex). In the

design of the anti-IgE mAb, several issues were considered.⁵⁴ First, the antibody should not bind to IgE that is bound to the FcεRI, which would lead to mast cell degranulation by cross-linking the receptor. Second, the IgE-anti-IgE immune complex should be biologically inactive and unable to activate complement or deposit in the tissue. Third, the antibody should not be immunogenic and elicit antibody production to the anti-IgE antibody itself. Finally, it should bind to IgE regardless of the specificity of the IgE molecule.

Selective binding of IgE requires that the mAb binds only to free IgE and not to IgE bound to FcεRI-FcεRII. By using homology scanning mutagenesis, a murine mAb that binds to the Cε3 portion of IgE, called MAE11, was constructed.⁵⁵ The MAE11 did not cross-link the receptor, which would have led to multiple biologic responses, possibly caused by anaphylaxis-induced mast cell degranulation. Furthermore, this selective binding prevents circulating IgE from binding to FcεRI. The mAb can bind to IgE, regardless of IgE specificities.

Clinical use of nonhuman antibodies in human subjects poses fundamental problems. Nonhuman antibodies are immunogenic, rapidly cleared, and usually demonstrate only weak recruitment of effector functions.⁵⁴ MAE11 was humanized with a human IgG1 framework to overcome these obstacles. It was found that only 5 changes in human framework residues were required to provide comparable binding with that of MAE11.⁵⁴ The humanized antibody rhuMAb-E25 contains approximately 5% nonhuman residues located at the complementary-determining regions.⁵⁴

Tissue distribution and complex formation with IgE and rhuMAb-E25 after intravenous administration was studied in cynomolgus monkeys.⁵⁶ No specific tissue deposition was seen. Pharmacokinetic analysis revealed that both rhuMAb-E25 and rhuMAb-E25-IgE immune complexes cleared the serum compartment, with urinary excretion as the primary route of elimination.⁵⁵ Elimination of the immune complex is mediated by the interaction with FcγR.^{55,57} Immune complex clearance is slower than IgE clearance, with a half-life of 3 weeks, and hence the total IgE level (IgE complexes with omalizumab and free IgE) is usually increased during omalizumab treatment, although free IgE levels decrease.

The largest immune complexes formed *in vivo* and *in vitro* are cyclic hexamers with a molecular weight of 1000 kD.⁵⁶ The size of the immune complex depends on the molar ratio of rhuMAb to IgE. At a 1:1 ratio, the cyclic hexamer formation was favored; at antibody or antigen excess, small heterotrimers were formed, with little detectable hexamer present at molar ratios of 3 or larger. There has been no significant association of rhuMAb-E25 or rhuMAb-E25-IgE immune complex with blood cells, and complement fixation is lacking.⁵⁶

OMALIZUMAB: CLINICAL APPLICATION

Several clinical trials have shown efficacy and safety in treating patients with allergic asthma and rhinitis with

omalizumab therapy. There is clinical evidence that treatment with an anti-IgE mAb might diminish peanut-induced allergic reactions in susceptible children. At the present time, omalizumab is indicated and approved for treating adults and adolescents (≥12 years of age) with moderate-to-severe persistent asthma who have a positive skin test response or *in vitro* reactivity to a perennial aeroallergen the symptoms of which are inadequately controlled with inhaled corticosteroid.

Clinical studies: Allergic asthma

The initial clinical studies in the late 1990s with omalizumab were performed in patients with mild allergic asthma. These studies found that treatment with omalizumab significantly attenuated both the early- and late-phase responses to airway challenge with specific allergens.^{58,59} Investigators observed both a reduction in the magnitude of the decrease in FEV₁ and an increase in the concentration of allergen (approximately 2.2 times more allergen) required to induce bronchoconstriction. Additionally, after 8 weeks of therapy, omalizumab decreased sputum eosinophils both before and after allergen challenge compared with baseline data.⁵⁸ Overall, these early studies suggested that treatment with omalizumab might have a significant effect on allergic asthma by influencing the early and late asthmatic responses to allergen.

The first large phase 2 clinical trial enrolled 317 subjects with moderate-to-severe asthma and compared the effect of intravenous omalizumab given at a low dose (2.5 μg/kg/ng of IgE/mL) and a high dose (5.8 μg/kg/ng of IgE/mL) with the effect of placebo.⁶⁰ The primary outcome, daily asthma symptom score, improved significantly by 42% in the high-dose treatment group compared with 30% in the placebo group. Additionally, a reduction in oral corticosteroid dose of greater than 50% was seen in 78% of the high-dose treatment group compared with 33% of the placebo group.

After these initial investigations, 3 phase 3, randomized, double-blind, placebo-controlled clinical trials have been completed, evaluating the effects of omalizumab in the treatment of patients with moderate-to-severe asthma.⁶¹⁻⁶⁴

Common among these trials is the study design and route of omalizumab administration. After initial screening, subjects were converted to beclomethasone dipropionate⁶¹⁻⁶³ for a 4- to 6-week run-in phase. Subjects were then randomized to subcutaneous treatment with either omalizumab (at least 0.016 mg/kg/IgE [IU/mL] every 4 weeks) or placebo for a total of 28 weeks. The first 16 weeks represented the steroid-stable phase, followed by a 12-week steroid-reduction phase. Subjects were then maintained at the lowest dose of corticosteroid for 4 weeks. Two of the study groups were followed up in a 24-week, double-blind extension phase.^{65,66} A fourth double-blind, randomized, placebo-controlled trial evaluated 246 adolescents and adults with controlled severe allergic asthma. The study design was similar to that of the above studies, with the exception that subjects were receiving high daily doses of fluticasone propionate (>1000 μg/d) instead of beclomethasone dipropionate.⁶⁴

TABLE I. Summary of the phase 3, randomized, double-blind clinical trials comparing omalizumab with placebo in the treatment of allergic asthma

	Omalizumab	Placebo	P value	Reference
Reduction of ICS dose by at least 50%*	100%	66.7%	<.001	Milgrom et al ⁶³
	72.4%	54.9%	<.001	Busse et al ⁶¹
	79%	55%	<.001	Soler et al ⁶²
	74%	51%	.001	Holgate et al ⁶⁴
Complete withdrawal of ICS*	55%	39%	.004	Milgrom et al ⁶³
	39.6%	19.1%	<.001	Busse et al ⁶¹
	43%	19%	<.001	Soler et al ⁶²
	21.4%	15%	.198	Holgate et al ⁶⁴
Equivalent dose of inhaled BDP during extension phase†	253 µg/d	434 µg/d	<.001	Buhl et al ⁶⁶
	227 µg/d	335 µg/d	<.001	Lanier et al ⁶⁵
Asthma exacerbations per patient (steroid-reduction phase)†	0.42	2.72	<.001	Milgrom et al ⁶³
	0.39	0.66	.003	Busse et al ⁶¹
	0.36	0.75	<.001	Soler et al ⁶²
Asthma exacerbations per patient (steroid-stable phase)†	0.28	0.54	.006	Busse et al ⁶¹
	0.28	0.66	<.001	Soler et al ⁶²
	0.15	0.23	NS	Holgate et al ⁶⁴
Asthma exacerbations per patient (extension phase)†	0.48	1.14	<.001	Buhl et al ⁶⁶
	0.60	0.83	.023	Lanier et al ⁶⁵
Patients with ≥1 asthma exacerbation (steroid-stable phase)†	12.8%	30.5%	<.001	Soler et al ⁶²
Subjects with ≥1 asthma exacerbation (steroid-reduction phase)†	15.7%	29.8%	<.001	Soler et al ⁶²
Subjects with ≥1 asthma exacerbation (extension phase)†	24%	40.6%	<.001	Buhl et al ⁶⁶
	31.8%	42.8%	.015	Lanier et al ⁶⁵
Missed days of school†	0.65	1.21	.04	Milgrom et al ⁶³

ICS, Inhaled corticosteroids; BDP, beclomethasone dipropionate.

*Median and †mean values are presented.

These clinical studies have evaluated a total of 1317 subjects aged 12 to 76 years^{61,62,64} and 334 children aged 6 to 12 years.⁶³ A reduction in median free IgE levels between 88% and 99% to approximately 5 to 9 IU/mL occurred with therapy compared with no change in subjects treated with placebo.⁶¹⁻⁶³ Results of these studies are outlined in Table I.⁶¹⁻⁶⁶ Overall, a reduction in inhaled corticosteroid was achieved without precipitating asthma exacerbations, worsening asthma symptoms and lung function, or increasing the use of rescue medication. Subjects who continued to be treated with omalizumab during the 6-month extension phase were able to maintain significantly lower use of inhaled corticosteroids compared with placebo.

A meta-analysis⁶⁷ of the adolescent and adult asthma studies^{61,62,64} were pooled to obtain a subgroup of 254 subjects at high risk of asthma-related morbidity and mortality. Results indicated that the annualized rate of significant asthma exacerbation episodes was halved by the addition of omalizumab to corticosteroid therapy. Specifically, the percentage of patients experiencing at least one significant asthma exacerbation episode was reduced from 35% (42/119) with placebo to 18% (24/135) with omalizumab. The mean rates per patient for a significant asthma exacerbation were 1.56 with placebo versus 0.69 with omalizumab ($P = .007$). The authors concluded that for every 100 high-risk patients treated with omalizumab for 1 year, 87 to 136 significant asthma exacerbation episodes might be prevented.

A second pooled analysis⁶⁸ of the initial 3 clinical trials in both children and adults⁶¹⁻⁶³ evaluated the rates of

serious asthma exacerbations between subjects treated with omalizumab compared with those treated with placebo. Overall, the incidence rate of hospitalizations for asthma was 92% lower in the omalizumab group than in the placebo group (omalizumab, 0.26 per 100 patient-years; placebo, 3.42 per 100 patient-years; $P < .002$). A lower incidence of serious asthma exacerbation that required unscheduled outpatient visits or emergency department treatments was also seen in the omalizumab-treated group.

A substudy of 35 subjects from 2 of the large clinical trials^{61,62} was conducted to correlate omalizumab therapy with changes in inflammatory mediators and clinical symptoms.⁶⁹ Markers of allergic inflammation, such as histamine release from basophils, blood eosinophil counts, and areas of wheal reaction to allergen skin prick tests, were all significantly decreased with omalizumab therapy compared with results with placebo. The only circulating mediator to significantly decrease was IL-13, although trends were observed for IL-5 and IL-8. There were no changes detected for IL-6, IL-10, or soluble intracellular adhesion molecule.⁶⁹ Anti-IgE therapy is also associated with a reduction in sputum and tissue eosinophils and reduced CD3⁺, CD4⁺, and CD8⁺ T lymphocytes; B lymphocytes; and cells staining for IL-4.⁷⁰

In addition to monitoring exacerbation rates and corticosteroid use, asthma control can be assessed by means of quality-of-life measurements. It has become increasingly apparent that physical, emotional, and social functional impairments occur in asthmatic patients that adversely affect patient lives. Furthermore, correlations between

TABLE II. Summary of the randomized, double-blind, clinical trials comparing omalizumab with placebo in the treatment of seasonal and perennial allergic rhinitis

	Omalizumab	Placebo	P value	Reference
Nasal symptom severity score*	0.75	0.98	.002	Casale et al ⁷⁸
	0.70	0.98	<.001	Adelroth et al ⁷⁹
	1.0	1.4	.001	Chervinsky et al ⁸⁰
Eye symptom severity score*	0.41	0.67	.001	Casale et al ⁷⁸
	0.43	0.54	.031	Adelroth et al ⁷⁹
Use rescue medication†	0.12	0.21	.005	Casale et al ⁷⁸
	0.59	1.37	<.001	Adelroth et al ⁷⁹
Rhinitis quality-of-life scores‡	44.1%	30.6%	<.01	Adelroth et al ⁷⁹
	52%	27%	.001	Chervinsky et al ⁸⁰
Total rhinitis quality-of-life score§	1.75	2.3	<.001	Adelroth et al ⁷⁹
Global treatment effectiveness	70.7%	40.8%	<.001	Casale et al ⁷⁸
	59%	35%	.001	Adelroth et al ⁷⁹
	53%	34%	.001	Chervinsky et al ⁸⁰
Missed days of work, school, or both	0.1	0.4	.005	Casale et al ⁷⁸

Mean scores are indicated.

*Range of possible scores is 0 (no symptoms) to 3 (worst symptoms).

†Average number of tablets per day.

‡Percentage of patients achieving clinically meaningful differences (≥ 0.5 change) in asthma quality-of-life questionnaire.⁸¹

§Five-point scale.

||Percentage of patients rating efficacy of treatment as good or excellent.

measures of clinical asthma severity and control and health-related quality-of-life impairment are only weak to moderate.⁷¹ The well-established and validated Asthma Quality of Life Questionnaire⁷² has been used to evaluate the treatment of omalizumab in patients with asthma. Several studies have shown that patients treated with omalizumab demonstrate clinically meaningful improvements in all asthma-related quality-of-life scores, as well as in overall scores, compared with results in patients treated with placebo.^{64,73-75} Notably, these studies also showed that quality-of-life improvement was maintained, even during the controlled attempts to reduce corticosteroid use.

Altogether, the above clinical studies suggest that therapy with omalizumab can have a major effect on the treatment of patients with moderate-to-severe allergic asthma. More importantly, omalizumab might be best used in the higher-risk patients who are at risk for serious asthma exacerbation requiring emergency department visitation, hospitalizations, or both.

Clinical studies: Allergic rhinitis

Allergic rhinitis does represent a large medical problem in the United States, affecting 20 to 40 million persons annually (10% to 30% of adults and close to 40% of children).⁷⁶ Although current therapies, such as intranasal corticosteroids, oral antihistamines, and antileukotrienes, are effective at reducing symptoms associated with allergic rhinitis, many patients still describe their symptom control as suboptimal.⁷⁷

Several studies have shown clinical efficacy and safety in the treatment of seasonal and perennial allergic rhinitis with omalizumab therapy. Large, randomized, double-blind, placebo-controlled trials have assessed therapy with omalizumab in the treatment of seasonal, ragweed-

TABLE III. Clinical efficacy of omalizumab in patients with allergic rhinitis and allergic asthma

Allergic rhinitis

- Reduction in daily nasal severity score
- Reduction in use of rescue antihistamines
- Improvement in quality of life
- Blunting of the seasonal increase of nasal symptoms during pollen season

Allergic asthma

- Reduction in early- and late-phase responses to allergen challenge
- Reduction in total asthma exacerbations
- Reduction in number of patients with ≥ 1 asthma exacerbations
- Reduction in dosage of ICS use
 - More subjects able to achieve complete discontinuation of corticosteroids
- Improvement in nocturnal asthma score
- Improvement in asthma quality-of-life score
- Reduction in hospitalizations—emergency department visits in high-risk asthmatic populations
- No significant change seen in FEV₁

ICS, Inhaled corticosteroid.

induced⁷⁸ and birch-induced⁷⁹ allergic rhinitis and perennial dust mite-, dog-, or cat-induced allergic rhinitis.⁸⁰ Common to all these studies is the finding that nasal symptom severity scores (sneezing, itchy, runny, and stuffy nose), use of rescue antihistamines, and rhinitis-specific quality-of-life scores were all significantly improved in patients receiving omalizumab therapy compared with those in patients receiving placebo. Table II⁷⁸⁻⁸¹ summarizes the results of these clinical trials. Further studies examining changes in the nose during therapy with omalizumab compared with placebo have found decreases in the number of inflammatory cells, including decreased

TABLE IV. Omalizumab dosage and dosing schedule on baseline total serum IgE and body weight*

Baseline serum IgE (IU/mL)	Body weight (kg)			
	30-60	>60-70	>70-90	>90-150
≥30-100	150 mg	150 mg	150 mg	300 mg
>100-200	300 mg	300 mg	300 mg	225 mg
>200-300	300 mg	225 mg	225 mg	300 mg
>300-400	225 mg	225 mg	300 mg	—
>400-500	300 mg	300 mg	375 mg	—
>500-600	300 mg	375 mg	—	—
>600-700	375 mg	—	—	—

Dosing is every 2 weeks for bolded values and otherwise every 4 weeks. Patients whose pretreatment serum IgE levels or body weights are outside the limits of the dosing table (>30 or >700 IU/mL and <30 and >150 kg) should not be dosed.

*Genentech Product Information.⁷⁰

eosinophil peroxidase–positive cells and decreased IgE⁺ staining cells.⁸²

A fourth large clinical trial examined the efficacy and safety of adding omalizumab treatment to polysensitized subjects (with birch and grass allergy) receiving maintenance specific immunotherapy (SIT).⁸³ After SIT maintenance was obtained, 4 treatment arms consisting of SIT-birch plus placebo, SIT-birch plus omalizumab, SIT-grass plus placebo, and SIT-grass plus omalizumab were evaluated. The groups receiving unrelated SIT were considered placebo control subjects during the appropriate allergy season. Overall, results demonstrated that combination therapy reduced symptom load during the 2 pollen seasons by 48% ($P = .001$). In the specific grass season symptom loads were also reduced. These results suggested that the addition of omalizumab to SIT reduced allergen-induced symptom load, regardless of the nature of the allergen and efficacy of conventional SIT.⁸³ In a substudy of this population, *in vitro* stimulation of leukocytes with grass or pollen allergens resulted in lower levels of sulfidoleukotrienes in the SIT plus omalizumab group compared with SIT alone.⁸⁴ In another analysis of this group, there was no difference in urinary leukotriene E₄ concentrations observed between treatment groups.⁸⁵

Compared with placebo, treatment with omalizumab has significantly affected the clinical indices associated with allergic rhinitis. An important concern is the cost-effectiveness of treatment with omalizumab for allergic rhinitis given the large number of patients with allergic rhinitis today. Identification of subgroups that would benefit most from therapy is necessary. Chervinsky et al⁸⁰ reported in a post-hoc analysis that patients who had previously failed to respond to immunotherapy achieved significantly greater reductions in nasal severity scores when treated with omalizumab. A second subgroup failing to respond to intranasal steroids also demonstrated improvement when treated with omalizumab. Rhinitis symptoms are commonly seen in patients with asthma. A population-based study recently reported that the prevalence of rhinitis was 50% to 77% in patients with asthma, and the prevalence of asthma was 7.6% to 22.6% in patients with rhinitis.⁸⁶ Currently, it does not appear financially practical to treat the millions of patients with allergic rhinitis with omalizumab; however, omalizumab

does represent a promising new therapy for the treatment of both allergic upper and lower airway diseases (Table III).

Clinical studies: Food allergy

To date, clinical studies investigating the effect of the anti-IgE mAb in regard to food allergy have been limited. A related compound to omalizumab, TNX-901, is also a humanized IgG1 mAb with similar biologic activity. In a randomized, double-blind, placebo-controlled, dose-ranging study, 84 patients with a history of immediate hypersensitivity to peanuts were evaluated.⁸⁷ At the highest dose (450 mg), TNX-901 significantly increased the threshold of sensitivity to peanut allergen, as evidenced by oral food challenge. Twenty-four percent of those in the 450-mg treated group were able to tolerate the highest level of peanut tested, which was 8 g. Although encouraging, use of an anti-IgE mAb for patients with a history of food allergen or anaphylaxis is not approved or indicated. More studies are needed to confirm these preliminary experimental results.

Clinical dosing

The goal of therapy with the anti-IgE mAb omalizumab is to reduce serum free IgE levels. In early clinical trials a relationship was demonstrated between clinical efficacy variables and free IgE concentrations, with the best results obtained when serum free IgE levels were less than 25 ng/mL or 10.4 IU/mL.⁸⁸ To achieve this goal, appropriate dosing depends on the subject's pretreatment serum IgE level (in international unit per milliliter) and weight (in kilogram), with a minimal dosing of 0.016 mg/kg (IU/mL) IgE per 4 weeks in divided doses as necessary. Table IV provides dosage information. Patients with pretreatment serum IgE levels or body weights outside the limits of the dosing table do not qualify for treatment because the volume of the drug would be too excessive and expensive.

Serum free IgE levels will decrease to approximately 1% of baseline values within 24 hours of subcutaneous administration.⁸⁸ Total serum IgE level (free plus bound) increases with treatment because of the formation of omalizumab-IgE complexes. Currently, measuring serum free IgE level is only available in research protocols, and therefore monitoring total serum IgE levels is not practical

and should not be done in a clinical setting once therapy is initiated.

Adverse events and safety

Omalizumab is nonallergen-specific and does not induce acute anaphylaxis because of the lack of IgE cross-linking with basophil- or mast cell-bound IgE. Furthermore, subcutaneous or intravenous administration of omalizumab does not generate anti-omalizumab antibodies.

Overall adverse events reported for subjects treated with omalizumab compared with placebo have been similar and categorized as mild to moderate in severity. The most commonly reported adverse events were fatigue, arthralgias, dizziness, itching, dermatitis, and injection-site reactions. In clinical trials to date, there has been no evidence of anti-IgE-IgE immune complex disease, nor has there been evidence of complement activation or fixation. The platelet abnormalities seen in a small segment of monkeys has not been seen in human trials.⁶⁵

Absolute contraindications to administration of omalizumab include a prior experience of severe hypersensitivity to omalizumab. The Food and Drug Administration warnings include concerns for malignancy and anaphylaxis.⁸⁹ Malignant neoplasms were observed in 20 (0.5%) of 4127 omalizumab-treated patients compared with 5 (0.2%) of 2236 control patients. The observed malignancies were of a wide variety, including breast, nonmelanoma skin, prostate, melanoma, and parotid. It is important to note the lower than expected rate of malignancy observed in the control group, which might account for the discrepancy between the groups.

Anaphylaxis occurred within 2 hours of the first or subsequent administration of omalizumab in 3 (<0.1%) patients without other identifiable allergic triggers. It is recommended that patients be observed after injection of omalizumab, with medications immediately available for the treatment of severe hypersensitivity reactions, including anaphylaxis.⁹⁰

CONCLUSIONS

Therapy with the anti-IgE mAb omalizumab represents a novel form of therapy in the treatment of allergic diseases. Statistically significant effects have been observed in the treatment of patients with both allergic upper and lower airway diseases. Omalizumab is safe and efficacious therapy when used in the appropriate clinical settings. As clinical experience grows with the use of omalizumab, more information will be learned about the mechanisms and effects of modulating IgE *in vivo*. At present, this form of therapy is best reserved for patients with a high risk of asthma morbidity and mortality.

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