



REVIEW ARTICLE

The pharmacological mechanisms of omalizumab in patients with very high IgE levels—Clues from studies on atopic dermatitis

Tse Wen Chang^{1,*}, Jiun-Bo Chen¹, Chia-Yu Chu²¹ The Genomics Research Center, Academia Sinica, Taipei 11529, Taiwan² Department of Dermatology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei 100, Taiwan

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ABSTRACT

Seventeen case series investigating the effects of omalizumab on patients with atopic dermatitis included patients whose pretreatment serum IgE was above 700 IU/ml, the upper inclusion limit specified in the product label. In all, 107 patients received omalizumab at doses of ≤ 375 mg every 2 weeks, which is recommended for patients with IgE < 700 IU/ml. Among them, 87 improved in clinical symptoms and some did so after the first dose. Among these 87 patients, 35 and 12 had pretreatment serum IgE in the range 700–7000 IU/ml and 7000–121,000 IU/ml, respectively. These results not only suggest the pathogenic roles of IgE and the potential utility of omalizumab in atopic dermatitis, but also raise questions concerning the pharmacological mechanisms of omalizumab in patients with very high IgE levels. If omalizumab at regular doses is proven to treat patients with ultra high IgE (e.g. above 7000 IU/ml) effectively, it probably achieves this without neutralizing most of the IgE produced in the patients and downregulating the high-affinity IgE-Fc receptors on basophils and mast cells. Herein, we propose that a potential main pharmacological mechanism of omalizumab in patients with ultra high IgE is the ability of the rapidly accumulated IgE:omalizumab complexes to trap allergens.

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Introduction

Anti-IgE antibodies, including omalizumab and TNX-901, are designed to bind to free IgE, but not to IgE bound by the high-affinity IgE-Fc receptors (FcεRI) on mast cells and basophils. These antibodies can neutralize IgE and block IgE binding to FcεRI, but cannot sensitize mast cells or basophils.^{1,2} A broadly adopted set of treatment protocols for the use of omalizumab were developed and have now been studied in more than 70 Phase II and III clinical trials in allergic asthma, allergic rhinitis, peanut allergy, chronic idiopathic urticaria, and other allergic indications.^{2–7} Omalizumab has been approved in the USA, the European Union, and many other regions for the treatment of patients aged 12 years and older with moderate-to-severe or severe allergic asthma.² It has also been approved for treating pediatric patients (aged 6–11 years old) with severe, persistent allergic asthma in the European Union since 2009.⁸

The guiding rationale in developing the anti-IgE therapeutic approach and in designing the treatment protocols is that free IgE in patients is nearly entirely neutralized by anti-IgE during the treatment period. The findings that the depletion of free IgE by omalizumab leads to the gradual downregulation of FcεRI on basophils and mast cells^{9–11} and dendritic cells¹² have reassured researchers and clinicians working with anti-IgE of the soundness of this new therapy for IgE-mediated allergic diseases. With such prevailing understanding of the anti-IgE approach, the overall positive results of case studies on treating patients with atopic dermatitis, chronic urticaria, allergic bronchopulmonary aspergillosis, and several other diseases, many of whom had very high serum IgE levels, with omalizumab doses designed for patients with normal to moderately high levels of IgE are unexpected. These results should prompt further evaluation of the pharmacological mechanisms of anti-IgE and the strict IgE-level-based inclusion criteria for use of omalizumab.

The IgE level-based protocols of omalizumab

IgE concentrations in allergic patients cover a very broad range. Based on the rationale that sufficient omalizumab is required to neutralize IgE present at the times of omalizumab administration

* Corresponding author. The Genomics Research Center, Academia Sinica, Taipei 11529, Taiwan. Tel.: +886 2 2787 1252; fax: +886 2 2789 8771.

E-mail addresses: twchang@gate.sinica.edu.tw (T.W. Chang), realleo@gmail.com (J.-B. Chen), chiayu.chu@gmail.com (C.-Y. Chu).

and produced during intervals between omalizumab administrations, dosing regimens were established empirically by measuring residual, unbound free IgE in test patients upon the administration of varying doses of omalizumab in several earlier studies.^{13,14} Such treatment regimens were further reinforced by a long series of later studies.^{15,16} It was determined that a monthly amount of omalizumab in mg equaling $0.016 \times \text{body weight in kg} \times \text{serum IgE concentration in IU/mL}$ was necessary to neutralize a patient's free IgE sufficiently. The approved protocols require that patients receive 150–300 mg omalizumab every 4 weeks or 225–375 mg every 2 weeks, based on patients' serum IgE levels and body weights.¹⁴ Under such protocols, patients with IgE levels above 700 IU/mL were generally excluded from the various clinical trials and patients eligible for medical payments by insurance companies and governmental health agencies generally must have IgE levels in the 30–700 IU/mL range (for patients with body weights of 70 kg or higher, the permissive IgE levels are stepwise lower).

Prescriptions for patients with IgE outside the approved IgE range are considered “off-label” uses. A significant proportion of patients with severe allergic asthma have IgE levels above the permitted limits. Those patients have been unfortunately excluded largely due to considerations over the cost of omalizumab. Conceptually, omalizumab should work in those patients, if additional amounts of anti-IgE are given, as was suggested by a recent study.¹⁶

Among patients with atopic dermatitis, the proportion with IgE above 700 IU/mL is much larger than that for adult allergic asthma: it is common to find atopic dermatitis patients with serum IgE even higher than 10,000 IU/mL.¹⁷ There have been no corporate-organized randomized, double-blind, placebo-controlled Phase II and III trials of omalizumab on atopic dermatitis, partly because of the concern that in many patients with atopic dermatitis, the IgE levels are too high to be neutralized by affordable doses of omalizumab.

Effects of omalizumab on atopic dermatitis

Since 2005, 17 case series investigating the therapeutic effects of omalizumab in patients with moderate-to-severe or severe atopic dermatitis patients have been published.^{18–34} In these reports, each studying 1–21 patients, 107 patients in total were treated with omalizumab at doses and schedules that were within or slightly above those approved for allergic asthma patients with IgE levels in the range of 30–700 IU/mL, as specified in the package insert of

omalizumab. The IgE levels of the 107 patients studied in the 17 reports, their dosing schedule with omalizumab, and clinical outcome after omalizumab treatment are summarized in Table 1.

The maximum dose of omalizumab employed for those 107 patients was 600 mg every 2 weeks, which lasted for 2 months, in the study of Park et al.²⁹ For some patients, even though their IgE levels were far above 700 IU/mL, they were given doses less than recommended for patients weighing 60 kg with serum IgE of 700 IU/mL. For example, the 11 patients studied by Belloni et al.,²¹ who had IgE levels in the range 1343–39,534 IU/mL, received 150 mg omalizumab every 2 weeks, which is less than the dose recommended for patients with IgE under 300 IU/mL with a body weight of about 70 kg. One case in the Lane et al report,¹⁹ with a serum IgE level of 2890 IU/mL, and four cases in the Toledo et al report³³ with serum IgE levels of 2058–35,346 IU/mL, were treated with 150 mg or 300 mg omalizumab every 2 weeks.

Among the 107 patients discussed in Table 1, 87 showed improvement of the clinical symptoms of atopic dermatitis. Among those 87 who improved as reported in 15 case series studies, 35 had pretreatment serum IgE levels of 700–7000 IU/mL, and 12 had IgE levels above 7000 IU/mL (range 7000–121,000 IU/mL). Among the 20 patients who did not improve with omalizumab treatment, most were from two reports. All three patients in the study of Krathen et al.¹⁸ did not improve in atopic dermatitis, although one case had improvement in asthmatic symptoms. Heil et al.²⁸ reported that all 13 patients in the treatment group did not show a significant improvement in clinical parameters as compared with the seven-patient placebo group.

These overall generally positive results of the 17 case series would have not been expected based on the current understanding that IgE must be neutralized almost completely over the entire treatment duration to prevent IgE from occupying FcεRI on basophils, mast cells, and dendritic cells and to maintain the down-regulation of FcεRI on those cells. Because the studies reported in these eight papers were open-label and not blinded, one should be cautious about placebo effects in evaluating such studies. Nonetheless, the results as a whole provide a certain degree of consistency: the number of independent reports and the total number of cases is relatively high. Many of the patients had had protracted disease histories and had taken various new drugs, and would probably not have had great expectation of the benefits of yet another new drug, omalizumab. In several of the studies, patients were scored at each visit, and gradual changes of symptoms were observed. There is sufficient evidence to indicate that the reported

Table 1 The list of case reports of omalizumab therapy on patients with atopic dermatitis.

References	No. of patients (F/M)	Mean age, y (range)	Mean serum IgE, IU/mL (range)	Dosing of omalizumab	No. of patients improved
Krathen et al. ¹⁸	3 (1/2)	39 (34–48)	17,613 (5440–24,400)	450 mg/2 wk	0
Lane et al. ¹⁹	3 (1/2)	12 (10–13)	3667 (1990–6120)	Varying	3
Vigo et al. ²⁰	7 (6/1)	32 (7–58)	1063 (265–2020)	300 or 375 mg/2 wk	7
Belloni et al. ²¹	11 (4/7)	37 (24–47)	15,095 (1343–39,534)	150 mg/2 wk	7
Forman et al. ²²	1 (0/1)	41	7340	375 mg/2 wk	1
Do et al. ²³	14 (8/6)	42 (14–60)	1158 (50–6981)	Varying	14
Sheinkopf et al. ²⁴	21 (12/9)	43 (14–62)	1521 (18–8396)	Varying	21
Incorvaia et al. ²⁵	1 (1/0)	39	1304	375 mg/2 wk	1
Amrol ²⁷	3 (1/2)	19 (6–36)	14,084 (1429–36,732)	300 or 375 mg/2 wk	3
Caruso et al. ²⁶	1 (1/0)	15	107	300 mg/4 wk	1
Heil et al. ²⁸	13 (8/5)	30 (18–47)	372 (205–5540) ^a	Varying ^a	0
Park et al. ²⁹	1 (0/1)	34	9360	600 or 300 mg/2 wk	1
Toledo et al. ³³	4 (1/3)	27 (15–35)	13,797 (2058–35,348)	Varying	4
Barrios et al. ³⁰	1 (1/0)	6	121,000	NS	1
Velling et al. ³⁴	9 (NP)	NS	3528 ± 2723	Varying	9
Thaiwat et al. ³²	3 (2/1)	33 (23–40)	490 (215.5–977)	300 mg/2 wk or 4 wk	3
Ramirez del Pozo et al. ³¹	11 (10/1)	12–52	NS	NS	11

NS = not stated in the article.

^a Provided by personal communication.

improvement in clinical scores was related to omalizumab and not due to placebo effects.

It has been suggested that some patients with atopic dermatitis are caused by intrinsic pathological factors, which are not mediated by IgE and may involve TH1 helper T cells.^{35,36} Thus, if these patients with “intrinsic atopic dermatitis” were excluded from the 107 patients in the 17 case series studies, the effects of omalizumab on the patients with “extrinsic atopic dermatitis” would have been even more pronounced. It should also be noted that IgE-mediated allergic reactions can occur in patients with very low serum levels of IgE, probably because allergen-specific IgE accounts for high proportions in total IgE in these patients.

Studies of omalizumab in high-IgE patients with other immune disorders

Herein, the results of case studies of omalizumab on other allergic diseases, which enlisted patients with serum IgE above 700 IU/mL among the recruited study patients, were also analyzed. Table 2 lists 15 case series study reports, including seven on allergic bronchopulmonary aspergillosis,^{37–43} two on idiopathic anaphylaxis,^{44,45} five on chronic urticaria,^{46–50} and one on food allergy.⁵¹ It should be noted that all 20 patients studied in those 15 case studies were severe patients and had been on various other medications. The clinicians treating those patients suggested omalizumab as a last alternative. All patients received omalizumab at 300 mg or 375 mg/2 weeks and 19 improved in their disease symptoms. Among these 19 patients, 18 had serum IgE levels in the 700–7000 IU/mL range, and one had serum IgE of 19,506 IU/mL shortly before the first omalizumab administration.

The definition of high and low dosages of omalizumab in relation to the intended IgE kinetics in the treated patient

The serum IgE levels vary in a broad range in patients with IgE-mediated allergic diseases. Among the 127 patients discussed in this paper, the IgE levels varied from 18 IU/mL (the lower limit of detection for the IgE assay) to 121,000 IU/mL. Thus, whether a dosage of omalizumab is considered high or low for a patient must be referenced against the serum IgE level of the patient, e.g.,

Table 2 The list of cases with serum IgE levels above 700 IU/mL who were treated with omalizumab for IgE-mediated disorders.

References	Disease	Sex	Age	Serum IgE, IU/mL	Dosing of omalizumab	Clinical improvement
van der Ent et al ³⁷	ABPA	F	12	5200	300 mg/2 wk	+
Zirbes et al ³⁸	ABPA	M	13	1064	300 mg/2 wk	+
		M	12.8	1075	375 mg/2 wk	+
Kanu et al ³⁹	ABPA	F	13	947	300 mg/2 wk	+
Lebecque et al ⁴¹	ABPA	M	14	4261	375 mg/2 wk	+
		F	14	1526	375 mg/2 wk	+
Randhawa et al ⁴⁰	ABPA	M	14	19,506	375 mg/2 wk	+
Lin et al ⁴²	ABPA	M	39	702	375 mg/2 wk	+
Sastre et al ⁴³	ABPA	F	33	3090	375 mg/2 wk	+
Boyce ⁴⁷	CU	F	12	1078	375 mg/2 wk	+
Spector et al ⁴⁶	CU	F	48	2257	375 mg/2 wk	+
Sabroe ⁴⁸	ChU	M	27	1523	300 mg/2 wk	-
Groffik et al ⁴⁹	CIU	F	67	2037	300 mg/2 wk	+
		F	49	4091	300 mg/2 wk	+
		M	41	1454	300 mg/2 wk	+
Ferrer et al ⁵⁰	CU	F	19	1940	300 mg/2 wk	+
Jones et al ⁴⁴	IA	M	48	1821	375 mg/2 wk	+
Warrier et al ⁴⁵	IA	M	12	1848	375 mg/2 wk	+
Rocha et al ⁵¹	FA	F	18	1890	300 mg/2 wk	+
		M	9	1470	300 mg/4 wk	+

ABPA = allergic bronchopulmonary aspergillosis; ChU = cholinergic urticaria; CIU = chronic idiopathic urticaria; CU = chronic urticaria; FA = food allergy; IA = idiopathic anaphylaxis.

a dosage of 150 mg/4 weeks can be considered a high dose for a patient with 10 IU/mL and a low dose for the patient with 30,000 IU/mL. The underlying rationale is that an applied regimen of omalizumab can achieve the pharmacological mechanisms that play roles in alleviating the allergic symptoms.

The pharmacological mechanisms of omalizumab, which contribute to the improvement of IgE-mediated allergic symptoms, are manifold. The binding of omalizumab to free IgE and the depletion of free IgE in the blood and in the interstitium not only inhibits the binding of IgE to FcεRI on basophils, mast cells, dendritic, and Langerhans cells, but also leads to the down-regulation of FcεRI on these cells. The inhibition of IgE binding to mast cells directly affects the survival of these cells. The down-regulation of FcεRI renders basophils and mast cells insensitive toward allergen activation, and Langerhans and dendritic cells are rendered less active in antigen presentation of allergens. The overall suppression of these various cell types reduces the levels of a wide spectrum of proinflammatory cytokines, and leads to the reduction of dendritic cells, lymphocytes, and eosinophils in mucosal tissues, eventually bringing down the inflammatory state of the entire immune system.⁵² The other series of effects may be derived from the interaction of omalizumab with membrane-bound IgE (mIgE) in BCR on mIgE⁺ B lymphoblasts and memory cells. While the effects of such interaction in patients treated with omalizumab are not well understood, a few studies indicate that anti-IgE has multiple effects on mIgE⁺ B cells *in vitro*.^{53,54} A recent study has found evidence that IgE production is decreased in patients treated with omalizumab.⁵⁵

Based on the above rationale, whether a dosage of omalizumab should be considered high or low should not be based in absolute quantities, i.e., in terms of mg/2 or 4 weeks. Instead, it should be referenced to its ability to neutralize free IgE in blood or interstitial fluids at the times of administration of omalizumab and during the intervals between omalizumab administrations. According to this concept, the dosages of omalizumab may be defined as high, medium–high, medium–low, and low dosages in relation to their ability to maintain free IgE levels near 0, as in Table 3. With a high-dosage regimen, free IgE is kept near 0 in the entire treatment period. With a low-dosage regimen, free IgE is never brought down to near 0 in the entire treatment period. With a medium-dosage regimen, free IgE is reduced to near 0 after an omalizumab dosing. However, there is not enough omalizumab to neutralize the free IgE produced during the interval before the next omalizumab dosing and hence free IgE starts to rise. As for how much free IgE will increase toward its pretreatment basal levels, it depends on how soon excess omalizumab will be consumed by neutralizing the newly synthesized IgE. In a medium–high dosing, after a number of dosing, omalizumab catches up to neutralize all IgE produced in the

Table 3 Definition of the relative dosages of omalizumab according to their abilities to neutralize free IgE at the time of administrations and during intervals between administrations.

Omalizumab relative dosage	Neutralizing free IgE		Kinetics of free IgE
	At administration	During intervals	
High	Yes	Yes	Omalizumab in excess; free IgE near 0 in the entire treatment period
Medium	Yes		Omalizumab in excess, IgE near 0 after each omalizumab dosing
High		No/Yes	IgE maintained near 0 after a number of omalizumab doses
Low		No	IgE near 0 intermittently in the entire treatment period
Low	No	No	Free IgE never near 0 in the entire treatment period

The dosage of omalizumab is relative to the IgE level in the administered patient.

intervals and thereafter free IgE is kept near 0 in the remaining treatment period. In a medium–low dosing, omalizumab never catches up to neutralize all the IgE produced in the intervals and free IgE is brought down to near 0 intermittently throughout the treatment period.

IgE is not entirely neutralized in some patients with very high IgE levels

In humans, IgE turns over with a relatively short half-life (2.4 days)¹⁵ and the long-living IgE-producing plasma cells residing in the bone marrow and mucosal lymphoid patches,⁵⁶ which express low levels of membrane-bound IgE and are not targets of omalizumab, continue to produce IgE to replenish the cleared IgE. In the approved protocols of omalizumab, which has a half-life of about 23 days,¹⁵ the antibody is administered in excess so that it is sufficient to neutralize all IgE present in the body at the time of the initial injection and produced during the 2- or 4-week intervals between injections. Conflicting data exist concerning whether anti-IgE can downregulate mIgE-expressing B lymphoblasts and memory B cells.^{21,53,57} If this mechanism occurs, the generation of new IgE-secreting plasma cells should be inhibited. However, existing plasma cells should not be affected by anti-IgE.

The dosing regimen of omalizumab required to neutralize all IgE sufficiently in a patient during a treatment period is related to: (1) the patient's basal IgE concentration and body weight; (2) the half-life (the rate of turnover and replenishment) of IgE and its volume of distribution; (3) the bioavailability of omalizumab in a subcutaneous administration, half-life, and its volume of distribution; and (4) the half-life IgE:omalizumab immune complexes, their volume of distribution, and the binding affinity of omalizumab to IgE. Because some of these variables vary widely among different individuals, e.g., the absolute bioavailability of omalizumab in a subcutaneous administration ranges from 53% to 71% (average 62%),¹⁵ the dosing protocols were established primarily by experimental measurements and not by calculation.¹⁴ It is understood that if omalizumab is under-dosed relative to the suggested amounts, free IgE may not be neutralized throughout the treatment period.

According to Hayashi et al.¹⁵, the average volume for distribution of IgE and omalizumab in a person is 5900 mL. This would mean that a person with 7000 IU/mL of serum IgE has about 91 mg of free IgE in the body, excluding IgE bound by cells (1 IU/mL = 2.4 ng/mL). The person would produce 263 mg of IgE in the 14 days between two omalizumab administrations (based on the half-life of IgE which is 2.4 days). Based on the bioavailability of omalizumab of 62% and that one omalizumab molecule can tie up two IgE molecules, an administration of 375 mg of omalizumab would yield about 233 mg, which is sufficient to neutralize all IgE present at the time of omalizumab administration. Since omalizumab has its own half-life of clearance, the amount remaining may not be sufficient to neutralize all of the IgE produced in the 14 days between omalizumab administrations.

Based on the above rationale, for patients whose serum IgE was near or above 7000 IU/mL, the omalizumab treatment regimens of 375 mg/2 weeks, while sufficient to neutralize all IgE present at the times of omalizumab administration, were insufficient to neutralize all of the IgE produced during the intervals between omalizumab administrations. In the study by Lim et al.,⁵⁸ an omalizumab regime of 150 mg/2 weeks was used for three patients, as used for the 11 patients in the study by Belloni et al.²¹ The administered omalizumab would not be enough to neutralize IgE present at the times of administration in many of the patients with IgE above 7000 IU/mL. In fact, free IgE levels were measured in the sera of some patients and found not to have changed.

Absence of IgE depletion does not lead to extensive FcεRI downregulation

The loss of FcεRI on basophils and mast cells is caused by the lack of occupation by IgE, because the unoccupied FcεRI are not stable and are rapidly internalized for degradation.⁵⁹ Basophils have a life span of 1–2 weeks and new basophils are generated constantly. When free IgE is nearly completely depleted, the FcεRI on the newly generated basophils are not occupied by IgE and are degraded at an accelerated pace. Thus, the numbers of FcεRI on basophils are downregulated appreciably in 1–2 weeks.^{9,10} Mast cells have a life span of several months or longer. When free IgE is low and omalizumab in large excess, the IgE molecules that dissociate from FcεRI due to thermodynamic equilibrium are trapped by omalizumab and hence the unbound FcεRI become unstable and degrade. Over time, the FcεRI on mast cells are also downregulated.

If free IgE is not almost completely neutralized for the entire duration in the intervals between omalizumab treatments, the FcεRI on basophils and mast cells are less likely to be extensively downregulated. Thus, the desensitization of those cells as a major mechanism of omalizumab is probably not responsible for the therapeutic effects observed in patients with ultra high IgE. Other mechanisms, such as a general depression of inflammatory state,⁵² which result from the inactivity of mast cells and basophils, would also not occur.

IgE and omalizumab form small immune complexes

An IgE molecule has two sites, on each of the two CH₃ domains, to be bound to by an omalizumab molecule and an omalizumab molecule has two Fab arms to bind IgE molecules. Theoretically, IgE and omalizumab molecules can form very large lattices and possibly aggregates or precipitates in patients. It is therefore a most

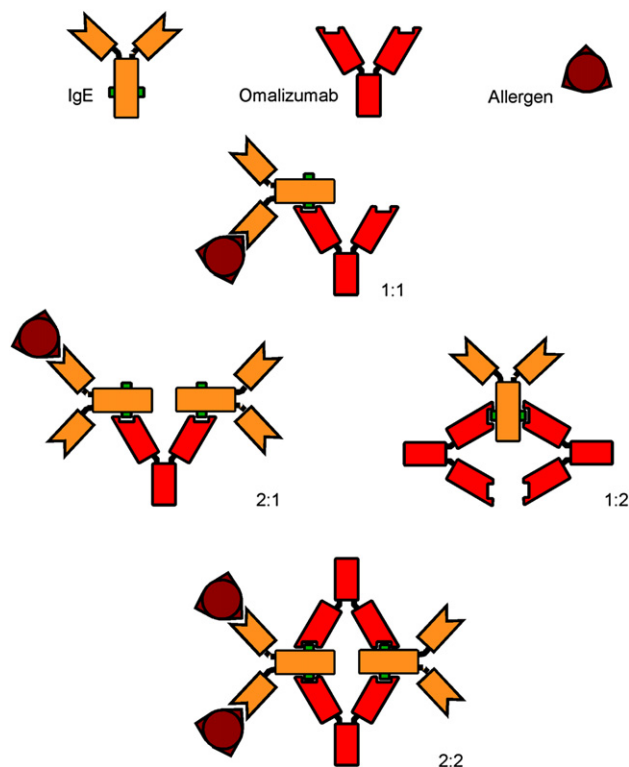


Figure 1 The complexes formed by IgE and omalizumab in various *in vitro* and *in vivo* conditions.

fortuitous fact that IgE and omalizumab form only small, soluble complexes in the blood of patients treated with omalizumab. In phosphate-buffered saline, IgE and omalizumab form *in vitro* complexes of 1:1, 1:2, 2:1, 2:2, and 3:3 (IgE:omalizumab) stoichiometry, but no larger ones.⁶⁰ The relative proportions of these complexes are related to the molar ratios of IgE and omalizumab. Similarly, in phosphate-buffered saline, CGP51901, a chimeric anti-IgE monoclonal antibody with a similar set of binding specificities toward IgE as omalizumab, and IgE formed heterotetramers (2:2) as the largest complex.⁵³ In a Phase I clinical study of CGP51901, most of the IgE was found to form heterotetramer complexes with CGP51901 (2:2) and no larger complexes in the patients treated with CGP51901.⁶¹ In a recently published study, it was found that IgE and omalizumab form complexes of various configurations in human serum *in vitro*, with the largest probably being heterotetramers (2:2 IgE:omalizumab) complexes.⁶² It was found that when IgE was in excess of omalizumab, 1:1 and 2:1 (IgE:omalizumab) species were primary structures; when omalizumab is in excess, 1:2 and 2:2 species were dominant; when IgE and omalizumab are comparable, all species were observed (Figure 1).

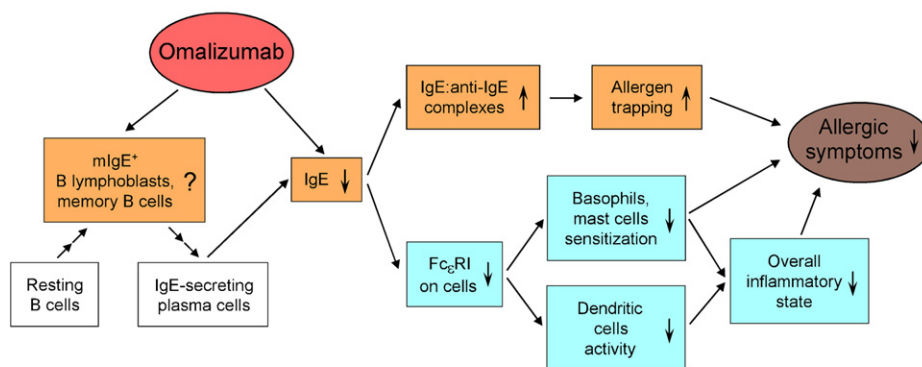
Existing evidence indicates that the IgE:omalizumab complexes do not bind to FcεRI, because even in the presence of secondary antibodies that cross-link anti-IgE, such complexes do not sensitize basophils.⁵³ Since the Fab arms of the IgE molecules in the immune complexes can still bind to their respective antigens, the immune complexes in fact can serve as protective allergen-capturing protective antibodies, similar to IgG specific for allergens.

IgE:omalizumab immune complexes probably play a key role in patients with very high IgE

The IgE:omalizumab immune complexes have an aggregate half-life in the range of 20–25 days.^{13,63} If omalizumab is constantly in excess of IgE, the continual replenishment of IgE by the IgE-secreting plasma cells will cause IgE:omalizumab immune complexes to accumulate to 2–3× basal IgE levels in 1 week and to nearly 10× in several weeks.^{13,63} When a treated patient's IgE is very high and the administered omalizumab is limiting, the accumulation of IgE:omalizumab complexes should occur each time immediately after the administration of omalizumab until it is exhausted.

Chang¹ recognized that the immune complexes cannot bind to the FcεRI on basophils and mast cells, but the allergen-specific IgE contained therein can bind to allergens that come into the immune system, and proposed that upon being bound by anti-IgE, the otherwise harmful allergen-specific IgE molecules are turned into protective antibodies, serving as allergen sweepers.¹ In an *in vitro* model, we have shown that human IgE:omalizumab immune complexes can trap allergens resulting in decreased allergen-induced degranulation and mediator release of transfected human FcεRI-expressing rat basophilic leukemic cells.⁶⁴ Even in cases where the omalizumab is administered to patients with IgE in the approved range (30–700 IU/mL), the accumulation of immune complexes should proceed faster than the downregulation of FcεRI on basophils and mast cells. In patients with very high serum IgE

A Patient's IgE neutralized



B Patient's IgE not neutralized

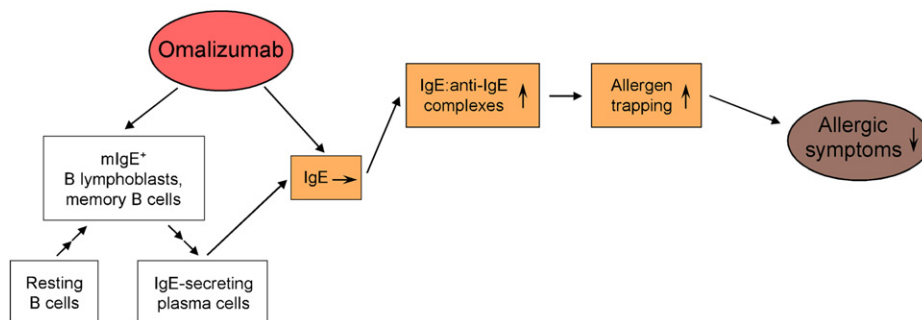


Figure 2 Possible immunological mechanisms of omalizumab at high or low dosages. The dosages are defined in relation to the patient's IgE level and in terms of whether IgE is neutralized completely, partly, or marginally during the treatment period, as explained in Table 3. Under a high-dose regimen, omalizumab is maintained in excess of free IgE and free IgE is entirely neutralized by anti-IgE during the treatment period. All of the effects in the blue and orange boxes probably occur. Under a low-dose regimen, free IgE is only neutralized partly at the time of the administration of omalizumab and IgE produced during the intervals of omalizumab administration is not neutralized. In this condition, one potential pharmacological mechanism is probably the trapping of allergens by the rapidly formed immune complexes (orange boxes).

levels (much above 700 IU/mL), the accumulation of IgE:omalizumab immune complexes will be even faster. As most allergen molecules are trapped, fewer of them can bind to FcεRI-bound IgE and sensitize basophils and mast cells. Furthermore, there will be reduced amounts of allergen to continue to drive the differentiation of naïve B cells into allergen-specific IgE-committed B cells and to induce the activation of allergen-specific IgE-expressing B cells.

Among the case series in Tables 1 and 2, the improvement of symptoms was observed in several cases after the first administration^{19,46} or the second injection.^{22,47,65} The primary inflammatory lesions in these allergic diseases are on skin or mucosal tissues of the respiratory tract and should involve mast cells. Since the downregulation of FcεRI on mast cells takes many weeks to several months,⁹ the proposition that the improvement is mediated by the trapping of incoming allergens by the accumulating immune complexes is plausible.

Figure 2 shows all of the potential pharmacological mechanisms of anti-IgE in a patient who was treated with omalizumab doses sufficient to neutralize all of the IgE during the treatment intervals. Almost all of those pharmacological effects were consequences of the depletion of free IgE. In cases where patients with ultra high serum IgE, e.g., near 7000 IU/mL or higher, are treated with anti-IgE at doses of 375 mg/2 weeks or less, the free IgE is not entirely neutralized, and many subsequent pharmacological effects will not occur. It appears that the mechanism still most likely to occur is the accumulation of IgE:omalizumab immune complexes and their trapping of incoming allergens.

Concluding remarks

The protective effect of the rapidly accumulated IgE:anti-IgE immune complexes in trapping allergens has been suggested to play a role in the pharmacological mechanisms of omalizumab.^{1,64} However, such an effect has been difficult to prove when administered anti-IgE can neutralize all IgE during the treatment period, because the depletion of free IgE leads to a host of other pharmacological effects, including the downregulation of FcεRI on basophils, mast cells, and dendritic cells, and a decrease in overall inflammatory status. In allergic patients with ultra high IgE, the administered anti-IgE could not neutralize all IgE during the treatment period and hence the various ensuing pharmacological mechanisms could have not occurred. It appears that a major potential pharmacological mechanism that can conceivably have occurred is the accumulation of IgE:omalizumab complexes and their trapping of allergens. If immune complexes do play a pharmacological role in patients with very high IgE, they should also play such a role in patients with IgE below 700 IU/mL, especially in the first few weeks after the first omalizumab administration, when the depletion of free IgE has not yet caused significant downregulation of FcεRI on mast cells. It will be of great interest to investigate whether immune complexes accumulate on the basal side of the mucosal epithelial layer where mast cells densely congregate and allergenic substances gain access to the body.

The results of the 17 case series studies discussed in this paper suggest that anti-IgE at doses established for patients with serum IgE below 700 IU/mL can effectively treat a portion of patients with atopic dermatitis, including those with serum IgE above 700 IU/mL. The beneficial effects of IgE:omalizumab immune complexes in sweeping allergens should also be present in high-IgE patients with allergic asthma or other allergic disease. The present paper thus encourages corporate-sponsored, organized Phase II and III trials of omalizumab in patients with atopic dermatitis and clinical trials of omalizumab in allergic asthma patients with serum IgE above 700 IU/mL.

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