

Review

Vaccines targeting IgE in the treatment of asthma and allergy

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Abbreviations: aa, amino acids; Cε, IgE constant domain; FcγRI, high affinity receptors for IgE; HBcAg, hepatitis B core antigen; HBsAg, hepatitis surface antigen; IL, interleukin; KLH, keyhole limpet hemocyanin; PCA, passive cutaneous anaphylaxis

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Allergic diseases including asthma are characterized by an increase of serum IgE levels. Since IgE was discovered in 1966, it has been considered to be the most important biological target in the treatment of allergy and asthma. Indeed, recent studies reveal that IgE, through its high affinity IgE receptors (FcεRI), is now considered a critical regulator of Th2 responses. This is supported by the great success of the anti-IgE monoclonal antibody (mAb) in the treatment of allergy and asthma. Nonetheless, adverse reactions such as anaphylaxis, urticaria and serum sickness have been reported with this therapy and repeated injections at extremely high costs are required to maintain effectiveness. To overcome these disadvantages, a new strategy using vaccines against IgE that may offer long-term efficacy with fewer adverse effects is being investigated. This article reviews IgE's role in allergy and asthma, currently used anti-IgE mAb omalizumab, and the advantages, types, effectiveness and development stages of vaccines against IgE. This review also discusses concerns with the vaccine strategy.

Background

Asthma and allergy. Asthma is one of the most common chronic diseases affecting approximately ten percent of the population.¹ Its prevalence has increased over the last few decades.²⁻⁵ Approximately two-thirds of asthma is allergic and >50% of patients with severe asthma have allergic asthma.^{6,7} In this review, "allergic asthma" is referred to as "asthma."

Asthma is an inflammatory disease of the airways, characterized by an increase of serum IgE levels, airway reactivity, mucus production and inflammation, finally leading to fibrosis and airway remodeling. These characteristics are associated with a predominant Th2 immune response. It has been proposed that the CD4⁺ T cells that produce Th2 cytokines, including IL-4, IL-5, IL-9 and IL-13 which upregulate IgE production, play a pivotal role in the pathogenesis of the disease.^{8,9} Although asthma is multifactorial in origin, the inflammatory process is believed to be a result of

inappropriate immune responses characterized by the increase of serum IgE antibodies to common aeroallergens in genetically susceptible individuals.

Serum IgE levels have been correlated with airway hyperresponsiveness both in adults^{10,11} and in children,¹² and is associated with the severity of asthma.¹³ It is well-established that the risk of developing asthma increases with increasing levels of serum IgE.¹¹ In addition to asthma, IgE is also responsible for allergic rhinitis, atopic dermatitis, adverse reactions to foods, medications, insect bites and stings and anaphylaxis, which are also increasing at an alarming rate.^{3,5,14}

Immunotherapies and biological agents in the treatment of asthma and allergy. Basic treatment for allergy and asthma includes (1) allergen avoidance, (2) pharmacological management that consists of sodium cromoglycate, inhaled corticosteroids, and histamine H1-receptor antagonists, etc. and (3) immunotherapy consisting of antigen-specific and non-allergen-specific approaches.¹⁵ The purpose of antigen-specific immunotherapy is to desensitize allergic subjects by repeated subcutaneous injections of small and gradually increasing amounts of the offending allergen. This therapy has been used for more than 100 years and is effective in the treatment of hay fever and venom allergy, but is less effective in asthma control.¹⁵ As most allergic subjects are sensitized to multiple allergens, non-allergen specific immunotherapy would be more effective in the treatment of these subjects. Overexpressed IgE and Th2 cytokines play important roles in the development of allergic inflammation; one intriguing strategy aims at limiting production of IgE and cytokines, or their accessibility to their respective receptors, so as to control the pathogenic process. To date, many new biological agents used as therapeutic modifiers have emerged as important new treatments. These include the administration of humanized monoclonal antibodies (mAbs) against such molecules or their receptors, soluble receptors, or mutated cytokines as passive blockers,¹⁶⁻¹⁹ as summarised in Table 1.^{16,20} Among these biological agents, the monoclonal antibody to IgE (omalizumab) has been proven to be effective in the treatment of asthma.

IgE and its high affinity receptor (FcγRI). Since IgE was discovered in 1966,²¹ it has been considered to be an important biological target in the treatment of allergy and asthma. IgE antibodies are known to play a major role in the development and regulation of asthmatic responses and are directly responsible for the allergic cascade.²² These allergen-specific IgE antibodies bind to high affinity

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receptors for IgE (FcγRI) on the surface of basophils, and mast cells, and other cells which includes human airway smooth muscle cells, antigen presenting cells (dendritic cells, Langerhans cells and monocytes), eosinophils, monocytes and macrophages, neutrophils and platelets.²³⁻²⁸

Upon re-exposure to the allergen and subsequent cross-linking of IgE via FcγRI, these cells are activated leading to the following phenomena: (1) mast cells and basophils are degranulated, releasing histamine and lipid mediators, which mediate immediate reactions, and cytokines (IL-4, IL-5, IL-13 and TNFα), which lead to late reactions (2) airway smooth muscle cell contraction is increased due to the markedly increased intracellular calcium concentration and secretion of Th2 cytokines (IL-4, IL-5, IL-13) and chemokines (eotacin-1/CCL1) that are important for the perpetuation and modulation of airway inflammation^{27,29} and (3) dendritic cells enhance antigen presentation to T cells, secrete several pro-inflammatory and chemotactic factors such as TNFα and MCP1, and skew towards a Th2-polarized response.²⁸

IgE upregulates the expression of FcγRI on these FcγRI bearing cells, leading to Th2 mediated inflammation and also mediates a significant survival effect on mast cells, neutrophils and monocytes through binding FcγRI.³⁰⁻³⁴ Thus, downregulation of IgE does not just reduce mast cell and basophil degranulation, it also suppresses Th2 inflammation mediated by those cells bearing FcγRI. Therefore, IgE is considered to have high potential as a target in the control of allergic asthma.

Monoclonal antibodies (mAb) targeting IgE. In an attempt to downregulate serum IgE, a recombinant humanized monoclonal antibody to human IgE named omalizumab (Xolair or E25) was developed. The mAb binds free, circulating IgE in the region of Cε3 and therefore blocks the binding of the free IgE to cell-membrane receptors. This inhibits the release of the mediators from mast cells and basophils and the activation of dendritic cells and other cells expressing FcγRI. The mAb does not bind to cell-bound IgE, so it does not trigger mast cell degranulation or dendritic cell activation.

Administration of the mAb in a number of large-scale, double-blind, randomized, placebo-controlled clinical trials suggests great benefits in patients with allergy and asthma. This treatment results in a significant improvement of symptoms including the reduction of exacerbation rates and medication use, improvement in lung function, and steroid-sparing effects, especially in those patients with severe and persistent asthma who have remained symptomatic despite treatment with systemic or inhaled corticosteroids.³⁵⁻⁴⁵ Its marked clinical efficacy is high with approximately two thirds of patients benefiting considerably.⁴⁰ Mechanism studies have revealed that this treatment not only reduces plasma free IgE levels, but also reduces FcγRI expression on basophils,⁴⁶ mast cells⁴⁷ and dendritic cells⁴⁸ to less than 5%.⁴⁹ In addition, the treatment reduces inflammatory cytokines such as IL-2 and IL-13,⁴⁴ and induces eosinophils apoptosis.⁴⁴ The multiple anti-inflammatory effects achieved by omalizumab further support that IgE is the right target in the treatment of asthma. In a recent issue of the European Respiratory Society, it is concluded that “the anti-inflammatory effects of omalizumab provide proof-of-concept of the key role played by IgE in allergic respiratory disease”⁵⁰ and “omalizumab addresses an unmet medical need in patients with severe persistent asthma symptoms, allowing these patients to live beyond the limitations of their asthma.”⁵¹

Table 1 Monoclonal antibodies (mAb) and receptor fusion proteins in the treatment of asthma

Name	Source	Target	Status
Omalizumab	Chimerical mAb	IgE	FDA-approved
Lumiliximab	Chimerical mAb	FcγRII/CD23	Phase II
Soluble IL-4 R	Fusion protein	IL-4	Phase II
Keliximab	Humanized mAb	IL-5	Phase II
Lumiliximab	Chimerical mAb	CD4	Phase II
Mepolizumab	Humanized mAb	IL-5	Phase II
Daclizumab	Humanized mAb	IL-2Rα	Phase II
CAT-354	Human mAb	IL-13	Animal model
IL-13Rα2-IgFc	Fusion protein	IL-13	Animal model
Infliximab	Chimerical mAb	TNFα	Phase II in asthma*
Etanercept	Fusion protein	TNFα	Phase II in asthma^
CAT-192,-152	Human mAb	TGFβ	Animal model#

*FDA-approved in Crohn disease and rheumatoid arthritis. ^FDA-approved in rheumatoid arthritis, ankylosing spondylitis, etc. #Phase II in systemic sclerosis.

Disadvantages of anti-IgE mAb. Omalizumab represents a novel reagent in the management of asthma. However, some significant disadvantages of this agent have limited its use. Because the agent acts as a passively administered antagonist, repeated injections with large doses are required to maintain the effects, as improvements seen are rapidly reversible upon discontinuation of the treatment. Due to its short half-life, the mAb to IgE, omalizumab, must be given intravenously or subcutaneously every 2–4 weeks at a dose of 200–400 mg/kg. The most serious adverse reactions observed in clinical studies with omalizumab are malignancies and anaphylaxis.^{18,52,53} The observed incidence of malignancy is 0.5%¹⁸ and the overall frequency of anaphylaxis is 0.2% in patients treated with omalizumab.⁵³ Severe serum sickness-like syndrome after omalizumab therapy has also been reported.^{54,55} Preliminary experience has reflected a consensus that “repeated urticarial reactions to omalizumab are a contraindication to the use of this therapy.”^{39,56} The number of cases in which therapy has been discontinued owing to urticaria is not known, reflecting the appearance of urticaria reactions in 1% or fewer injections.⁵² Another highly relevant concern is the extremely high cost associated with such passively administered therapeutics. The estimated cost for omalizumab is between \$6,492 and \$32,742 per year per patient (see www.aafp.org/afp/20050115/steps.html). In the long term, the cost of downregulating airway allergic responses using the passive blockage will be huge, because asthma is a chronic, life-long disease that is most often first diagnosed before the age of five.

Active immunization with vaccines against overexpressed endogenous molecules. To overcome these disadvantages, a new strategy that may offer long-term efficacy with fewer adverse effects is being investigated.^{57,58} In this approach, auto-antibodies against self-IgE or cytokines are induced by using vaccines (Fig. 1). Based on providing effective T cell help, two broad experimental strategies have been used to design such vaccines: (1) to modify the intact self-protein by inserting a foreign peptide containing Th epitopes⁵⁹ or (2) to chemically couple or fuse the intact self-protein,⁶⁰⁻⁶³ or a considerable part thereof,⁶⁴ to an immunogenic carrier protein.

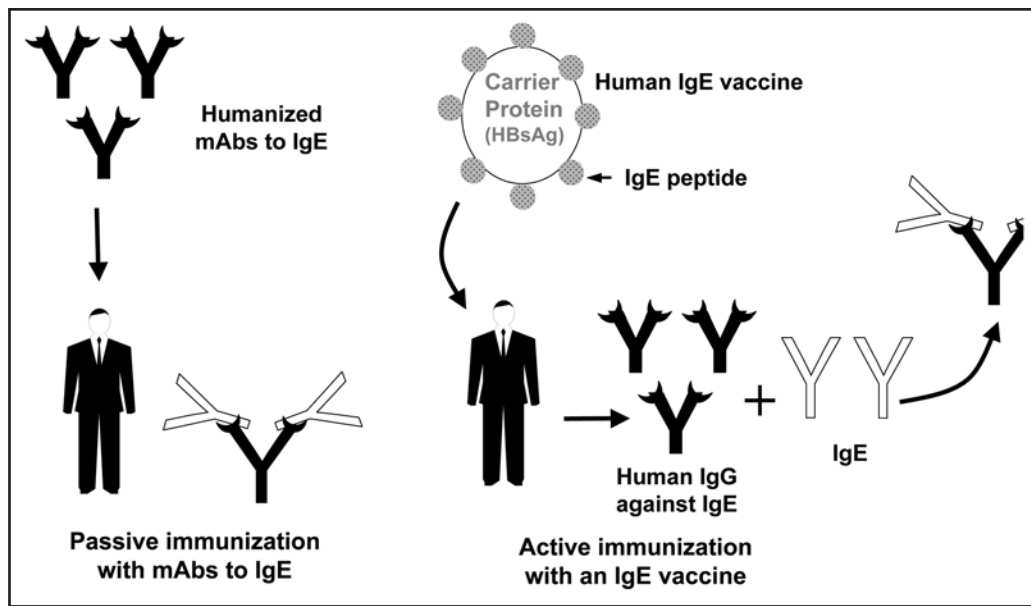


Figure 1. Passive immunization with monoclonal antibodies to IgE and active immunization with an IgE vaccine.

Polyclonal antibodies induced by such vaccines, which are against multiple self-antigen determinants, may cross-react with other self-proteins that contain similar epitopes. This is of particular concern when this strategy is used in humans. Although peptide-based vaccines have been investigated by chemically coupling self-peptides to a carrier protein (keyhole limpet hemocyanin), such vaccines do not present as virus-like particles and therefore have low immunogenicity, requiring strong adjuvants (complete Freund's adjuvant) to elicit sufficient immune responses.^{62,65} Recent studies have shown that the virus-like particle has unique advantages as a vaccine carrier, representing a safe and effective vaccine platform for inducing potent B and T cell responses. Virus-like particles have been used previously to induce auto-antibodies to disease-associated self molecules involved in chronic diseases.⁶⁶⁻⁶⁸

Vaccines against IgE

In 1985, Marshall and Bell successfully induced autoantibodies against self IgE by two intraperitoneal injections of 100 µg of purified alum precipitated rat myeloma IgE (IR2) in rats.⁶⁹ The rat anti-IgE antibodies bound to rat myeloma IgE IR2, a second myeloma IR162, and to mouse monoclonal IgE, but not to IgG. Administration of the alum precipitated rat myeloma IgE reduced subsequent specific IgE responses⁷⁰ and skin mast cell degranulation⁷¹ in rats. Their work confirms that auto anti-IgE antibodies, which reduce IgE-mediated allergic responses, can be induced. Since then, vaccines targeting IgE have been further investigated. Table 2 summarizes the types of IgE vaccines.

Chimeric IgE vaccines. IgE vaccines were reported by coupling or fusing a significantly large portion of rat IgE (whole Cε2 and/or Cε3) to a heterogenous carrier protein (either the glutathione-S-transferase protein⁷² or opossum Cε2 and Cε4⁶⁴) forming a chimeric IgE molecule⁷² or a fusion protein.⁶⁴ In the fusion protein, the target rat Cε3 was inserted between opossum Cε2 and opossum Cε4, forming a fusion protein "ORO." To enhance the immunogenicity, a variant of the IgE vaccine was constructed by

repeating the "ORO" structure to "ORORO."⁷³ Administration of the IgE vaccine in ovalbumin-sensitized rats resulted in anti-rat IgE antibody responses and in a substantial reduction of serum IgE that corresponds to a 92% reduction.⁶⁴

Although these vaccines induced strong anti-self-IgE responses, the polyclonal antibodies to IgE induced by the vaccine act against all epitopes in the target Cε2 and/or Cε3, which may cross-react with other immunoglobulins containing the same epitopes.

IgE peptide-KLH and -other foreign peptide vaccines. IgE peptide-based vaccines were reported in 1990.⁷⁴ This type of IgE vaccine minimizes possible cross-reactivity because the peptide sequences used are short and are IgE specific. A peptide (10 amino acids) derived from human IgE Cε4 was synthesized and chemically conjugated to a carrier KLH. The antiserum, obtained from rabbits immunized with the conjugate, was able to inhibit histamine release from rat mast cells. Immunization of sensitized rats with the conjugate reduced histamine concentrations and abolished egg white-induced anaphylactic reactions in response to egg white challenging.⁷⁴

Later in 1997, synthesized peptides derived from human IgE Cε3 and Cε4 were chemically conjugated to a carrier KLH.^{75,76} The rhesus monkeys immunized with the conjugate were subsequently protected in a passive cutaneous anaphylaxis (PCA) test when sensitized with human IgE and triggered with the corresponding allergen (i.e. the human IgE used for passive sensitization was neutralized by the serum anti-IgE antibodies). Mice, fed by intragastric gavages with bacteriophages displaying the small IgE-homologous structures, produced serum anti-IgE antibodies.

More recently, selected IgE peptides from various species were synthesized and made immunogenic either by chemical conjugation to KLH, or by covalent attachment to promiscuous Th epitopes and other immunostimulatory sequences by continuous synthesis.⁶⁵ In the study, a human IgE peptide, modified from positions 413–435 of a loop region of Cε3, was linked to a combinatorial Th epitope derived from hepatitis B virus or later, derived from measles virus.⁶⁵

Table 2 Vaccines targeting IgE

Description of vaccine	Status	In vivo results	Author/year
Alum precipitated rat myeloma IgE	Rats	Reduced subsequent IgE responses and skin mast cell degranulation	Marshall JS and Bell EB. 1985, 1989; Marchall et al., 1987
Conjugate a human IgE peptide to KLH	Rabbit, rats	Reduced serum histamine concentrations and anaphylaxis reactions	Stanworth DR, et al., 1990
A chimeric IgE molecule containing rat Cε3 domain and opossum Cε2 and Cε2 domains	Rats	Reduced serum IgE levels	Hellman L, 1994; Vernersson M, et al., 2002
Conjugate human IgE peptides to KLH	Monkey	Vaccinated monkey serum inhibited passive cutaneous anaphylaxis induced by human IgE	Stadler BM, 1999
Conjugate IgE peptides of various species to KLH	Dogs, rats	Reduced histamine release and serum IgE levels	Wang CY, et al., 2003
Conjugate 3 human IgE peptides to HBsAg	Rats, mice	Prevented IgE production and reversed elevated IgE in sensitized rats and mice	Peng Z, et al., 2007

This vaccine was shown to induce polyclonal site-specific anti-IgE antibodies that obstruct binding to FcγRI, inhibit histamine release from IgE-sensitized basophils, inhibit PCA, and do not signal degranulation.⁶⁵ Immunized dogs experienced significant reductions in total serum IgE.⁶⁵

IgE peptide-based virus-like particle vaccines. The antigenicity of either the chimeric IgE vaccine⁶⁴ or the IgE peptide-based vaccines^{65,74} described above are not strong, requiring the addition of the strong adjuvant CFA/IFA that cannot be used in humans to elicit anti-IgE responses.

As discussed in the section on active immunization, the virus-like particle has unique advantages as a vaccine carrier.⁶⁸ Recently, a human IgE peptide-based virus-like particle vaccine has been reported. Three peptides (³⁴⁵PFDLFIRK³⁵², ³⁷¹NLTWSRASGKPVNHST³⁸⁶ and ⁴⁰⁷TRDWIEGETYQC⁴¹⁸) were selected from human IgE receptor-binding sites located in Cε3 domain. The vaccine was made by coupling the three synthetic peptides to the carrier protein hepatitis B surface antigen (HBsAg) using the glutaraldehyde method to form a vaccine conjugate.⁷⁷ Sera from vaccine-immunized rats contained high titers of antibodies which reacted with soluble and plate-bound human IgE (Table 3).⁷⁷ As the peptides are derived from IgE receptor binding sites, the antibodies induced by the vaccine did not react with receptor bound IgE, suggesting that the antibodies do not cause histamine release from basophils or mast cells.⁷⁷ The sera also cross-reacted with mouse, rat and dog IgE with low titers (Table 2).⁷⁷ Furthermore, the sera inhibited the binding of human IgE or mouse IgE to its receptor in a dose-dependent manner as shown by ELISA, flow cytometry analysis and PCA tests.⁷⁷

Because the human IgE peptide-based vaccine cross-reacts with mouse and rat IgE at low titers, the in vivo effect of the vaccine was tested, as a test of principle, in trichosanin (TKM)-sensitized rodents. The results were very encouraging. Even though the vaccine induced low titers to rat (1:1,000) and mouse (>1:8,000) IgE, the responses were still sufficient to prevent the increase of TKM specific-IgE levels and to downregulate the specific IgE levels that were already elevated in sensitized mice and rats to levels between 8% to 32% of control levels (Fig. 2). This suggests that administration of the IgE vaccine is a potential therapeutic approach in the treatment of allergy and asthma.⁷⁷ It is anticipated that mouse or rat IgE peptides, in the form of virus-like particle vaccines, will also break down B cell tolerance. A rat or mouse IgE peptide-based

Table 3 Serum IgG titers to human IgE and the IgE of dogs, rats and mice in rats immunized with the human IgE vaccine

Test serum	Anti-human IgE	Anti-dog IgE	Anti-mouse IgE	Anti-rat IgE
Rat #1	800,000	32,000	8,000	2,000
Rat #2	200,000	64,000	8,000	1,000
Rat #3	200,000	32,000	8,000	500
Rat #4	200,000	32,000	8,000	1,000

vaccine would be an important contribution to the field and should be undertaken in future studies.

Discussion

Virus-like particles vaccines. There are different types of vaccines against self molecules as discussed in the active immunization section. Among them, the peptide-based and virus-like vaccines seem to have unique advantages due to the virus-like particle HBsAg that is used as a carrier in the vaccine and to the self peptides used in the vaccine. This allows minimum possible cross-reactivity to other self-peptides. Although adjuvant had been used in the IgE study,⁷⁷ recently data from the same laboratory have shown that administration of the virus-like particle vaccine induced high and long-lasting immune responses to the target self-protein even without the use of any adjuvant.^{66,67} These large particles are highly antigenic because they improve the presentation of the epitopes to cells of the immune system. Immunization with the self-peptides displayed on the surface of a virus-like particle has been proven to produce high titer antibodies to the self-antigen.^{66,67,78,79} In addition, the carrier HBsAg protein itself is an approved human vaccine component with an approximate 20-year license and safety record in the market, making this IgE vaccine valuable in human use.

Advantages of IgE vaccines compared with anti-IgE mAb. The following are the advantages of this novel strategy: (1) Long-lasting—it provides long-term protection with a few injections, as asthma is a chronic immunological disorder, requiring long-term treatment; (2) Low costs—the vaccine itself is less costly and the amount required to elicit immune responses will be much less in comparison to the omalizumab currently being used; (3) Less adverse reactions—as the

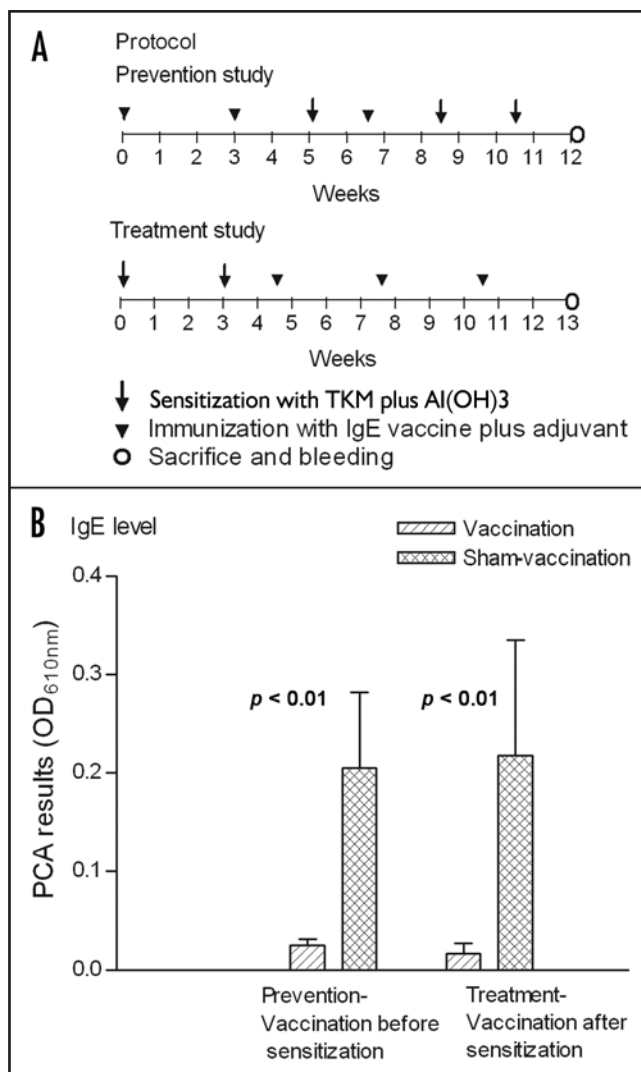


Figure 2. The effect of immunization with an IgE peptide-based vaccine in the downregulation of serum Trichosanthin (TKM)-specific IgE levels in rats. Wistar rats (4 each group) were subcutaneously immunized with the vaccine in Novasome adjuvant at week 0, 3 and 6 (100 µg/rat for the first immunization and 50 µg/rat for subsequent immunizations) three times before (for the preventive study) or after (for the treatment study) sensitizations commenced. Sensitization was achieved by 2–3 times intraperitoneal injections with TKM pollen (400 µg in 10 mg of alum/rat for the first injection and 200 µg in 10 mg of alum/rat for subsequent sensitizations). Rats receiving the carrier protein, HBsAg, served as controls. One week after the final sensitization, rats were sacrificed and serum samples were measured for TKM-specific IgE using passive cutaneous anaphylaxis (PCA) tests.

vaccine is given intramuscularly or subcutaneously, no infusion reactions will occur. Further, the anti-IgE antibodies are natural human antibodies and therefore the development of antibodies against the infused mAb will not occur; and (4) Prevention of asthma—as the adverse reactions in IgE vaccination are relatively few, this strategy might be also useful to serve as a prophylactic protection for children who are at a high risk of developing allergic asthma. Table 4 summarizes and compares the differences of the two immunization approaches.

Concerns on the strategy using IgE vaccines. Compared with

cytokine vaccines such as IL-13 and IL-4, IgE vaccines are safer as IgE is the terminal product of the allergic process and involves mast cells, basophils and airway smooth muscle cells, eosinophils, etc.²³⁻²⁸ These cells have less immune regulatory functions than the lymphocytes regulated by IL-4 and IL-13 cytokines. There are concerns regarding the consequences of consistently inhibiting IgE, because some studies indicate that IgE may be important in the immune defense system against helminth infections.^{80,81} However, other studies found that anti-IgE treatment decreases worm burden and egg production in parasite-infected mice.^{82,83} Indeed, induction of autoantibodies against IgE by alum precipitated rat myeloma IgE induced an accelerated elimination of *N. brasiliensis* from small intestines of infected rats.⁸³ Studies of patients with parasitic infections reveal an inverse correlation between serum IgE concentration and severity of reinfection or the number of the parasite larvae.⁸⁴⁻⁸⁶ A recent report indicates that in humans infected with *Trichinella*, *Trichinella*-specific IgE antibody is responsible for allergic manifestations that are typical of the clinical picture of Trichinellosis, but not for a protective role.⁸⁷ Most importantly, studies with anti-IgE therapy show that there is no increase in parasitic or other infections.^{37,38,88} In the case that this treatment increases the risk of some parasite infections, which are very few in North America, we can certainly treat the infection with anti-parasite drugs.

As to the risk of inducing Th1-mediated autoimmune diseases, it has not been demonstrated that enhancement of a Th2 cytokine response will ameliorate or prevent these disorders.⁸⁹ Another concern of the IgE vaccine strategy is the possibility of emergence of type III hypersensitivity reactions due to the formation of immune complexes. The chance of inducing type III hypersensitivity is unlikely for the following reasons: (1) Unlike the omalizumab therapy that requires a large amount of mAb quickly injected intravenously, in the vaccine strategy, the long-lasting anti-IgE antibodies induced by the host can neutralize IgE on a daily basis. Therefore, the small amounts of anti-IgE and IgE immune complexes formed would be easily cleared out by the immune system right away. Even in the omalizumab treatment, immune complex-induced adverse reactions have not been reported; (2) The concentration of IgE in the serum (<1 µg/ml) is extremely low compared to IgG, IgM, IgA and IgD, and, also, the half-life of serum IgE is much shorter than other isotypes (about 2 days compared with 21–23 days for IgG);⁹⁰ and (3) As the decrease of IgE levels reduces FcγRI expression on basophils,⁴⁶ mast cells⁴⁷ and dendritic cells⁴⁸ to less than 5%,⁴⁹ it is anticipated that vaccinated subjects will have less IgE production when they are triggered by exposures to the allergen.

The other concern is that once the anti-IgE antibodies are induced, it may be not easy to turn them off if the treatment is no longer required. In contrast to conventional microbe vaccines, vaccines against self-molecules such as IgE and cytokines trigger only transient (3–4 months), not life-time, high titers of antibodies neutralizing pathogenic cytokines.⁵⁸ The titers are found to be reversible and to drop by 80–90 % six months after the last vaccination with a TNFα vaccine in mice.⁹¹ In another study, the titers of IL-13-specific IgG induced by immunization with an IL-13 vaccine last for 5–6 months in mice and are significantly increased by a booster injection.⁶⁶

The above concerns need to be further investigated. It should be balanced against the benefits of treatment and the very real and often severe side effects of conventional therapies.

Table 4 A comparison of passive immunization with monoclonal antibodies (omalizumab) and active immunization with IgE vaccines

	Passive immunization with mAb	Active immunization with vaccines
Antigen	Antigen not required	IgE derivatives
Antibody	Chimeric mAb Contains 5% mouse IgG sequence Monoclonal	Natural human antibodies 100% of humans Polyclonal
Administration	Injected s.c. or i.v. Every 2–4 weeks	s.c. 2–3 times at 2-week intervals boosters may be required
Dose	Large dose (5 mg/kg)	Very low
Start time	Immediately	1–2 months later
Duration of effect	Short term (2–4 wk)	Long term (>4 months)
Adverse reactions:	Infusion reactions Serum sickness Development of anti-mAb antibodies Anaphylaxis Delayed hypersensitivity Possible malignancy	Not applicable Not applicable Not applicable Unlikely Unlikely
Cost	Extremely high cost	Perhaps the same as mAb Low cost
Clinical use	Therapeutic for acute asthma	Therapeutic for chronic asthma Preventive for children at a high risk of developing asthma (?)

Summary and Overall Significance

The prevalence, morbidity and mortality of asthma have increased dramatically over the last few decades despite the increased use of currently available therapies. As allergic asthma is an immunological disorder in nature, immunologically downregulating the levels of IgE should be a better approach for treatment than currently pharmaceutical therapies because it specifically targets the pathogenic molecule. When compared with currently used monoclonal antibody omalizumab, the proposed new strategy has the opportunity to provide a long-lasting impact on the treatment of asthma and allergy, especially to life-threatening, severe asthma, with fewer side effects. With the omalizumab therapy and the new strategy of IgE vaccines, maximum benefits for patients with different manifestations of asthma and allergy may be achieved, as omalizumab can be used in acute asthma, while IgE vaccine would be suitable for chronic cases.

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