

Will Anti-IgE Therapy Compromise Normal Immune Functions?

by Bob Q. Lanier & Tse Wen Chang

Background: The emergence of the novel therapeutic humanized anti-IgE antibody (omalizumab), which acts in part by tying up the immunoglobulin E (IgE) antibody class, has given pause for reexamination of the essential functions of IgE. In particular, will anti-IgE therapy open up the human body to complications such as parasite infections and cancer, and adverse events involving other entities newly introduced by its administration?

Methods: A detailed survey and analysis of (a) the studies that investigate the possible roles of IgE on the defense against parasites and malignancy, (b) the results relating to adverse events observed during the clinical studies of anti-IgE antibodies, in which more than 6,000 patients received the drugs, and (c) the experience of over 20,000 human patients who have received omalizumab since its United States commercial launch in July 2003.

Results: The IgE-mediated immune mechanism seems to have a modest role in the protection of human subjects against the infection of parasitic worms since the defense function is handled by several redundant immune mechanisms. In addition, the risk of infection by those parasites is low for people living in regions where sanitary conditions have been improved. The evidence that IgE is involved in the defense against cancer is very weak.

Conclusion: The neutralization of IgE by an anti-IgE therapeutic does not compromise the overall immune function. Anti-IgE is safe in the treatment of human allergic diseases.

Keywords: anti-IgE therapy, omalizumab, parasites, malignancy

Allergy Clin Immunol Int – J World Allergy Org 2004; 16:xxx–xxx

mark of the most frequent form of hypersensitivity reactions (type I), anaphylaxis, and most allergic diseases. Conversely, IgE has often been attributed an important role in the defense against parasite infection. There is also a sporadically expressed notion implicating the role of IgE in the protection against cancer. A therapeutic anti-IgE monoclonal antibody [1–6], which depletes IgE and consequentially brings about immunoregulatory effects in patients, is in relatively wide use by moderate and severe asthmatic patients within a year of its approval in the US. The drug is also being actively developed for allergic rhinitis and peanut allergy. These pharmaceutical advances warrant our revisiting the benefits of IgE and examination of the potential complication of anti-IgE in compromising normal immune function.

IgE as a Major Mediator of Allergic Reactions

The association of the entity now known as IgE as a villain in health dates back to the early 1800s when London physicians first described “hayfever.” Blakely demonstrated the association of pollen to the condition by simple abrasion skin tests in 1873 and produced the first laboratory test reflecting at least the level of bound IgE on mast cells. The reaginic properties of the circulating entity causing allergy was demonstrated initially in 1921 by Prausnitz and Kustner as the PK phenomenon, and lives on as the favorite trivia question among immunology students “Who had fish allergy – Prausnitz or Kustner?” It was, of course, Heinz Kustner who experienced urticaria and an anaphylactic response to the ingestion of fish. In the classic experiment, serum was transferred from Kustner to the abdominal skin of Carl Prausnitz who was not allergic to fish. When Prausnitz ingested fish, he urticated at the site of the serum injection indicating the transfer of the entity responsible for allergy – possibly an antibody.

Until the 1960s, this antibody was thought to be a subset of IgA. However, anti-IgA would not defeat the physiologic effects of the studied entity, indicating something biologically new and

The initial impression of the student of immunology for the most recently discovered antibody class is generally negative. Immunoglobulin E (IgE) is well known for being a central mediator in the sensitization of mast cells and basophils, a hall-

distinct. Bennich and Johansson discovered a myeloma protein in 1965 which demonstrated properties consistent with the allergic entity. Using this rich source, a polyclonal anti-IgE was developed. Together with the Ishizaka group in Denver, SGO Johansson and colleagues in Uppsala used this tool and other techniques to confirm and announce the discovery of the allergic antibody, IgE [7, 8]. Allergists, initially skeptical, became intrigued as cell bound IgE was shown to initiate histamine release and produce the most common immune disturbance of humans.

It had long been established that IgE is a central mediator of type-I hypersensitivity reactions and involved in the pathogenesis of allergic rhinitis. However, while elevated serum IgE levels have been known to be associated or correlate with the risk of “extrinsic” or “allergic” asthma, the involvement of IgE in the pathology of allergic asthma had not been clear until a series of human clinical studies of omalizumab over the past decade clearly showed that by neutralizing IgE, the early and late-phase reactions associated with the development of asthmatic symptoms could be ameliorated [3–5, 9–11]. With the help of clinical studies of omalizumab and TNX-901 (both humanized anti-IgE antibodies with a similar set of binding specificities toward human IgE, it is also clear that IgE plays a central role in allergic or anaphylactic reactions to foods and latex and that anti-IgE is effective in treating those types of allergic reactions [6, 12]. Whether IgE plays a major role in atopic dermatitis remains to be investigated.

Potential Beneficial Roles of IgE in Immune Defense

Protection Against Parasites

The requirement of IgE in parasitic protection seems most convincing in the defense against helminth infections, such as schistosomiasis and strongyloidiasis [13–16]. Despite many years of research in delineating the roles of IgE in clearing a parasite infection, the most supportive evidence lies largely in the correlation between IgE levels and the timing of parasite infection. The involvement of IgE varies according to the life cycle of the invading parasites, their physical location and duration. Indeed, many parasites invoke little IgE response at all.

Acute helminth infections evoke a mixed T-helper cell types 1 and 2 (Th1/Th2) cytokine response, marked eosinophilia, and high levels of parasite-specific IgE, causing urticarial rash, angioedema, and wheezing. These allergic reactions are uncommon in chronic infection as the response shifts to an almost complete Th2 with high levels of immunosuppressive cytokines such as interleukin-10 (IL-10) and transforming growth factor- β (TGF- β). IgE levels tend to be much higher in chronic infections and less parasite specific [17]. IgE contributes to the immediate response and parasite-directed inflammatory reac-

tions of antibody-dependent cellular cytotoxicity, but whether the mast cell release of cytokines is actually important in the killing of parasites in humans is unclear at this point.

Unlike the other four antibody classes and other components in human blood and tissue, which are generally present in rather defined ranges, IgE exists in an extremely broad range from less than a few nanograms to more than a few micrograms per milliliter in serum, with some individuals with normal immune function having very low or even undetectable serum IgE levels. These observations seem to suggest that IgE does not play an essential role or even a beneficial role but is dispensable and its roles can be filled by other immune mechanisms when it is absent. This analysis is consistent with the results that in a one-year trial of patients treated with anti-IgE, the depletion of IgE did not affect the incidence and severity of disease associated with the reinfection of ascariasis [18].

More important in total consideration of parasites is their potential role in the immunomodulation of the clinical presentation of allergy. Parasites invoke a strong regulatory environment, which could have far reaching implication as they are systematically wiped out in the western world, leading many to believe the balance of parasites and allergy is an important one. Indeed, those most deeply involved in their eradication now wonder whether such activity is as beneficial as they once thought [19].

Protection from Neoplasia

There exists a poorly documented notion among some physicians that allergic people may be more resistant to certain forms of cancer. This concept was probably initiated by a report by Cockcroft and colleagues in 1979, which summarized a comparative survey of 392 patients with three types of malignancy and 303 controls and concluded that the patients with endodermal neoplasia (lung, gut, bladder, prostate) had lowered forms of allergic disease [20]. In the study by McWhorter and coworkers [16], 6,913 patients with smoking, asthma, hayfever, hives, or food allergy, concluded the contrary – that allergic patients had a slightly higher risk odd ratio (1.4) for developing some types of malignancy [21]. The major weakness of those surveys was that the sample sizes were too small to be significant. In another study done on a population of 78,000 asthmatic patients in Finland [22], it was found that such patients have higher standardized incidence ratios with lung (1.32–1.6), colon (1.28), and rectal cancer (1.17), and lower ratios with stomach cancer (0.88) and leukemia (0.55). In summary, there are insufficient studies in the literature to suggest that allergy or IgE protects against cancer.

An in-depth analysis of the data concerning the occurrence of tumors among patients treated with omalizumab is especially pertinent. Malignancies were found in 20 of 4,127 patients (0.5%) exposed to anti-IgE, compared to 5 of 2,236 patients (0.2%) exposed to placebo, which on the surface might cause concern. However, a further analysis found that the vast majority of the 20 cases occurred in an older patient population, which were not matched with controls, and that at least 5 of the 20 had

the same cancer before exposure to anti-IgE (their being admitted to the trial with existing cancer must be considered a gross error in protocol adherence for the investigators). The time of exposure to anti-IgE was too short for the tumors to be induced and to grow to the substantial sizes reported. The tumors found were of seemingly random distribution of ectodermal, endodermal, and mesodermal categories. These various observations have led a panel of hemoncologists in a preliminary, blinded analysis to suggest that there should be no concern for causation of malignancy by anti-IgE.

Potential Adverse Effects of Anti-IgE

While the risks of parasitic infection and neoplasia associated with the use of anti-IgE therapy seem negligible with the analyses made so far, there remain some concerns. These concerns arise mostly from two potentially imperfect aspects of the properties of therapeutic anti-IgE. Firstly, the antibody may not be strictly specific for human IgE and hence can bind to other components in the blood or on certain types of cells. Secondly, the antibody is not entirely human and may not be regarded as an autologous molecule by the immune system in some patients.

Potential Reactivity with Platelets

The high-affinity IgE receptor, FcεRI, and the low-affinity IgE receptor, FcεRII, are present on cells other than mast cells, basophils, and activated eosinophils [23]. In an earlier toxicology study, some juvenile monkeys were found to develop severe thrombocytopenia when given high doses of E26, an experimental humanized antibody structurally modified from omalizumab. The mechanism of action was not well understood, because omalizumab was screened for its inability to bind to IgE that is already bound by FcεRI. Nevertheless, it was suggested that the depletion of the platelets by E26 in the tested animals, which could be inhibited by the administration of intravenous immunoglobulin (IVIg), was due to Fc receptor-mediated phagocytosis of platelets. Further studies have indicated that the adverse effect is related to E26 and to certain nonhuman primates. It is possible that E26, which was designed to have a much higher affinity for human IgE than omalizumab, acquired binding activity toward certain surface components on monkey platelets [27].

Careful examination of the safety data from the clinical trials reveals that in 98% of omalizumab-treated patients ($n = 2,614$) and 99.3% of placebo-treated patients, platelet counts decreased on one occasion by less than $150 \times 10^9/L$, considered within the a normal range. In phase I/II clinical trials, 11% of patients treated with omalizumab were found to have a bleeding-related event (ecchymosis, epistaxis, hemoptysis, menorrhagia, metrorrhagia, patechaie/patechial rash) compared to 6% of placebo-treated patients. No adverse event in the omalizumab-treated group was considered to be associated with the drug itself [28].

Potential Complication Due to Immune Complexes

Anti-IgE binds to free IgE and forms dimer, trimer, and hexamer complexes, but no larger lattices or complexes [24]. The long-living IgE-secreting plasma cells, which express very low levels of membrane-bound IgE and are not targeted by omalizumab, continue to produce IgE in patients treated with omalizumab. Because both omalizumab and the IgE:omalizumab complexes have half lives of about 20 days and IgE has a half life of 1–2 days, the immune complexes may accumulate to more than ten times the basal levels of IgE. The persistence of these complexes is noted for as long as one year following discontinuation of use of omalizumab. Since the immune complexes are small and soluble and their concentrations are within the normal ranges of immune complexes in the blood, they do not fix complement, attract phagocytes, and hence do not cause inflammation and immune complex disease [2].

IgE:omalizumab immune complexes, while unable to bind to IgE receptors, can still bind to allergens and may function like protective allergen-specific IgG and serve as an allergen buffer [2]. This potential beneficial effect of anti-IgE may provide important pharmacological roles in the initial period after the administration of anti-IgE since it will take several weeks for the FcεRI on mast cells to be significantly downregulated [25].

In clinical trials, particular attention was paid to inflammation-related adverse events (regardless of drug relationships), including pruritis, fever, lymphadenopathy, malaise, flu-like syndrome, and arthralgia. In pooled data of phase I/II studies, 1.3% of omalizumab-treated patients experienced one or more of these symptoms compared to 2.3% of placebo-treated patients. Thus, these adverse events were not considered drug related and did not recur with continued treatment.

Anaphylactic Reactions

More than 6,000 patients received omalizumab or TNX-901 during the clinical trials of these two drugs in the past 13 years. Three cases of systemic reactions in omalizumab-treated patients were reported, although the designation of “anaphylactic” was not strictly accurate, since no diagnostic tests (serum tryptase) were performed. The time frame from injection of omalizumab to reaction varied from 30–120 minutes, with one reaction occurring 90 minutes following the first exposure.

Theoretically, in view of the fact that a relatively high proportion (13.1%) of people in a studied US population have pre-existing sensitivity to mouse antigens [26], mouse sensitivity could play a role in a reaction with a recombinant antibody containing 5% sequence of murine origin (almost entirely the complementarity-determining regions).

It is estimated that since omalizumab was launched in July 2004, more than 100,000 injections of the drug have been administered to more than 20,000 patients with asthma. No case of serious adverse event, such as anaphylaxis and severe bleeding, has been published.

Summary

A humanized anti-IgE antibody, omalizumab, was recently launched in the US for the treatment of adult and adolescent patients with moderate to [word missing, CHECK] asthma. Since its introduction in July 2003, more than 20,000 patients have been using the drug. This new therapeutic is also being actively studied as a treatment for allergic rhinitis, sensitivity to peanuts, and other allergic diseases. Because anti-IgE is designed to neutralize the entire IgE class, concerns arise whether the therapeutic will cripple the normal immune functions IgE otherwise has, such as the function in protection against parasite infection and the potential function in protection against malignancy.

An in-depth analysis of the existing literature, the results of numerous human clinical studies carried out so far, and the lack of serious adverse incidences among the users of omalizumab, has led us to suggest that the beneficial functions of IgE are already covered or can be substituted by other immune mechanisms of the highly redundant immune system and thus that IgE is dispensable. We also suggest as a corollary that anti-IgE will not compromise the immune functions of patients. Nonetheless, continual monitoring of potential adverse events among the increased users of omalizumab is reasonable.

References

- [1] Davis FM, Gossett LA, Pinkston KL, Liou RS, Sun LK, Kim YW, Chang NT, Chang TW, Wagner K, Bews J, et al. Can anti-IgE be used to treat allergy? *Springer Semin Immunopathol* 1993; 15:51–73
- [2] Chang TW. The pharmacological basis of anti-IgE therapy. *Nature Biotechnol* 2000; 18:157–162
- [3] Busse W, Neaville W. Anti-immunoglobulin E for the treatment of allergic disease. *Curr Opin Allergy Clin Immunol* 2001; 1:105–108
- [4] Lanier BQ. Newer aspects in the treatment of pediatric and adult asthma: Monoclonal anti-IgE. *Ann Allergy Asthma Immunol* 2003; 90:13–15
- [5] Casale TB. Omalizumab: An effective anti-IgE treatment for allergic asthma and rhinitis. *Drugs Today* 2004; 40:367–376
- [6] Leung DY, Shanahan WR Jr, Li XM, Sampson HA. New approaches for the treatment of anaphylaxis. *Novartis Found Symp* 2004; 257:248–260
- [7] Ishizaka K, Ishizaka T. Identification of gamma E-antibodies as a carrier of reaginic activity. *J Immunol* 1967; 99:1187–1198
- [8] Johansson SGO, Bennich H. Immunological studies of an atypical (myeloma) immunoglobulin. *Immunol* 1967; 13:381–394
- [9] Babu KS, Holgate ST. The role of anti-IgE therapies in the treatment of asthma. *Hosp Med* 2002; 63:483–486
- [10] Johansson SGO, Haahtela T, O'Byrne PM. Omalizumab and the human immune system: An overview of preclinical and clinical data. *Ann Allergy Asthma Immunol* 2002; 89:132–136
- [11] Lanier BQ, Corren J, Lumry W, Liu J, Fowler-Taylor A, Gupta N. Omalizumab is effective in the long-term control of severe allergic asthma. *Ann Allergy Asthma Immunol* 2003; 91:154–159
- [12] Leung DY, Sampson HA, Yunginger JW, Burks AW Jr, Schneider LC, Wortel CH, Davis FM, Hyun JD, Shanahan WR Jr; Avon Longitudinal Study of Parents and Children Study Team. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 2003; 348:986–993
- [13] Capron A, Dessaint JP. Immunologic aspects of schistosomiasis. *Ann Rev Med* 1992; 43:209–218
- [14] Rihet P, Demeure CE, Bourgois A. Evidence for an association between human resistance to *Schistosoma mansoni* and high anti-larval IgE levels. *Eur J Immunol* 1991; 21:2679–2686
- [15] Neva, FA. Biology and immunology of human stongyloidiasis. *J Infect Dis* 1986; 153:397–406
- [16] Negrao-Correa D. Importance of immunoglobulin E (IgE) in the protective mechanism against gastrointestinal nematode infection: Looking at the intestinal mucosae. *Rev Inst Med Trop Sao Paulo* 2001; 43:291–299
- [17] McCarthy JS, Ottesen EA, Nutman TB. Onchocerciasis in endemic and nonendemic populations: Differences in clinical presentation and immunological findings. *J Infect Dis* 1994; 170:736–741
- [18] A 52-week treatment, multi-center, randomized, double blinded, parallel group controlled study to investigate the effect of omalizumab on intestinal geohelminth reinfection in adolescent patients with allergic asthma and or perennial allergic rhinitis previously treated with an anti-intestinal geohelminth treatment regimen. Brazilian Ascariasis Reinfection Trial – CIGE025a 2303. Novartis data on file
- [19] Hagel I, Di Prisco MC, Goldblatt J, Le Souef PN. The role of parasites in genetic susceptibility to allergy: IgE, helminthic infection and allergy, and the evolution of the human immune system. *Clin Rev Allergy Immunol* 2004; 26: 75–84
- [20] Cockcroft DW, Klein GJ, Donevan RE, Copland GM. Is there a negative correlation between malignancy and respiratory atopy? *Ann Allergy* 1979; 43:345–347
- [21] McWhorter WP. Allergy and the risk of cancer. *Cancer* 1988; 62:451–455
- [22] Vesterinen E, Pukkala E, Timonen T, Aromaa A. Cancer incidence among 78,000 asthmatic patients. *Int J Epidemiol* 1993; 22:976–982
- [23] Joseph M, Gounni AS, Kusnierz JP, Vorng H, Sarfati M, Kinet JP, Tonnel AB, Capron A, Capron M. Expression and functions of the high-affinity IgE receptor on human platelets and megakaryocyte precursors. *Eur J Immunol* 1997; 27:2212–2218
- [24] Corne J, Djukanovic R, Thomas L, Warner J, Botta L, Grandordy B, Gygax D, Heusser C, Patalano F, Richardson W, Kilchherr E, Staehelin T, Davis F, Gordon W, Sun L, Liou R, Wang G, Chang TW, Holgate S. The effect of intravenous administration of a chimeric anti-IgE antibody on serum IgE levels in atopic subjects: Efficacy, safety, and pharmacokinetics. *J Clin Invest* 1997; 99: 879–887
- [25] MacGlashan DW Jr, Bochner BS, Adelman DC, Jardieu PM, Togias A, McKenzie-White J, Sterbinsky SA, Hamilton RG, Lichtenstein LM. Down-regulation of FcεRI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol* 1997; 158:1438–1445
- [26] Matsui EC, Wood RA, Rand C, Kanchanaraks S, Swartz L, Eggleston PA. Mouse allergen exposure and mouse skin test sensitivity in suburban, middle-class children with asthma. *J Allergy Clin Immunol* 2004; 113:910–915
- [27] Omalizumab: Anti-IgE IGE monoclonal antibody E25, E25, humanised anti-IgE MAb, 025, monoclonal antibody E25, Olizumab, Xolair, rhuMAB-E25. *BioDrugs* 2002; 16(5):380–386
- [28] Novartis/Genetech data on file

Bob Lanier, MD (to whom correspondence should be addressed) is Clinical Professor of Pediatrics at the University of North Texas Health Science Center, 6407 Southwest Blvd., Fort Worth, TX 76132, USA (tel. +1 817 731-9198, fax +1 817 731-9199, e-mail boblaniermd@askdrbob.com)