

Unanswered clinical questions and speculation about the role of anti-immunoglobulin E in atopic and nonatopic disease

Bob Lanier, M.D.

ABSTRACT

As clinical experience with omalizumab increases, questions arise from clinicians that are not answered in the product insert or clinical reports. How does this drug really work? There surely must be more than the simple reduction of free IgE which, in and of itself, causes no disease. Can omalizumab be used in patients whose IgE level is below 30 or above 700 IU/mL? Can you treat a pregnant asthmatic woman with omalizumab? What are the updated risks for cancer? Is there a risk for omalizumab-treated patients who travel to parasite-endemic areas? What are the implications of skin-prick tests that remain positive after treatment? Does this drug prevent anaphylaxis with enough assurity to use it in conjunction with immunotherapy (IT) or rush IT? Are the complexes formed as a result of therapy problematic, therapeutic, or inconsequential? How long should this drug be used? It is the purpose of this review to examine these clinical issues and present common strategies for approaching each. (Allergy Asthma Proc 27:S37–S42, 2006)

As clinical experience with a commercially available anti-immunoglobulin E (IgE) agent omalizumab (Xolair, Genentech) increases, questions inevitably arise that are neither answered in the product insert of the drug nor that can be found in most literature citations. The purpose of this presentation is to examine these critical issues and offer some common strategies for their solution.

HOW DOES ANTI-IgE WORK?

The mechanism of action of anti-IgE so elegantly described by Soresi and Togias¹ in this Supplement is extremely critical to physicians entrusted to the care of patients with allergic disease, because it provides the basis and direction for proper dosing, profiling, and evaluation of successful treatment as well as length of therapy. Nonetheless, it is clearly evident that the generally accepted explanation for the bicameral mechanism of action of anti-IgE, *i.e.*, decreasing free IgE and down-regulating mast cell receptors suggested in the original approval process, is incomplete.

The suggested dosing level suggested is designed to reduce the free serum IgE levels below 10 IU/mL. However, it should be pointed out that free IgE does not cause disease, that its reduction does not produce relief in and of itself, and that down-regulation of FcεR1 receptors may merely be a reflection of reduced free IgE levels. Therefore, although lowered free IgE levels and receptors are certainly effects of anti-IgE treatment, they may not necessarily be a mechanism of action. Eventually, a clearer understanding of the mechanistic action of this agent should help extricate

us from the lock-step dosing regimen that continues to guide its current use. The recent studies of Dr. T.W. Chang², described in this Supplement, suggest that anti-IgE may have an effect on the B cell itself.

WHAT ABOUT THE USE OF ANTI-IgE IN ASTHMATIC PATIENTS WITH TOTAL IgE LEVELS >700 IU/mL?

The original concept of dosing was based on weight versus free IgE levels and used a dosage of 0.016 mg/kg per IU of baseline serum IgE concentration. For ease of calculation and to minimize the possibility of dosing errors, the computations were converted into a dosing table using a range of serum IgE levels ranging from a low of 30 IU/mL to a high of 700 IU/mL. Although a useful guide, issues arose (primarily legal not scientific) for patients who did not fit the dosing table described in the package insert.

Patients with slightly higher levels of IgE or those with greater weight do not fit the dosing table. Those who do not fit the criteria because of weight are “covered” by the “maximum” dose of 375 mg every 2 weeks (even though this runs counter to the generally accepted mechanism of action, *i.e.*, reduction of serum IgE leading to reduction of IgE receptors). However, patients with serum IgE levels >700 IU/mL are rejected routinely for consideration for therapy, prompting physicians to ask, “Why can’t I use the 0.016-mg/kg formula from which the table was derived?” “What are the dangers of levels >700 IU/mL that would give me pause to treat a severe asthmatic patient who meets the other criteria?”

The use of high doses requiring the use of multiple vials was discouraged for fear of the accumulation of minute amounts of endotoxin that accompany all biological products and the production of local or systemic reactions. Physicians concerned about that possibility re-

From the Department of Pediatrics, University of North Texas, Fort Worth, Texas
Address correspondence and reprint requests to Bob Lanier, M.D., Department of Pediatrics, University of North Texas, 6407 Southwest Boulevard, Fort Worth, TX 76132
E-mail address: boblaniermd@askdrbob.com
Copyright © 2006, OceanSide Publications, Inc., U.S.A.

acted by giving smaller dosages more often than 2 weeks so that no individual shot has more than the maximum dosage. There has been no published or abstracted evidence of endotoxin accumulation or reactions with a more frequent dosage or even larger doses in the usual frequency. However, the approach to very high IgE levels in asthmatic patients is problematic because most of the serum IgE in patients is nonspecific or "nonsense," making large doses less than efficient because only a modicum of the free IgE is relevant clinically.

Physicians also have questioned the wisdom of raising the serum IgE (as reflected by complexes of IgE and anti-IgE) to enormous levels *via* complexes. If the general observations of an expected rise in serum IgE is three to five times the baseline, a patient starting with 2000 IU/mL could have, after treatment, a serum level of 10,000 IU/mL or more. We know that the majority of complexes in the usual range are heximers and trimers, but we do not have good studies of the environment when very high levels of IgE exist. There are no published reports or abstracts proving a good clinical response in asthmatic patients with very high IgE. However, preliminary research done in atopic dogs shows improvement in dermatitis in animals with extremely high serum IgE levels.³ Dermatitis in the human still has not paralleled the canine experience.⁴

Physicians do have the ability to use omalizumab "off label," but the seas are uncharted. Although most physicians are clinically unconcerned about using the agent in lower than recommended dosages, they feel less comfortable using higher dosages.

WHAT ABOUT THE USE OF ANTI-IgE IN PATIENTS WITH TOTAL IgE LEVELS <30 IU/mL?

Because the stated and approved purpose of therapeutic anti-IgE is to lower the free IgE level, there was initially little enthusiasm for attacking processes having already low total IgE levels despite the established observation that many patients with obvious, indeed life threatening, food, insect, and latex allergy, and asthma, may have "normal" or "low" total levels of IgE. Low IgE levels may be more important in some asthmatic patients, artificially lowered levels secondary to chronic steroid use are seen.^{5,6} For the clinician and asthmatic patient, the process of application for insurance coverage for potential anti-IgE therapy is frustrating if the minimum IgE level of 30 IU/mL is mandatory for initial consideration.

Publications and abstracts have appeared suggesting that some individuals with <30 IU/mL have good responses with anti-IgE treatment in latex and peanut sensitivity.^{7,8} The progress of these patients and others has called into question the primary goal of anti-IgE therapy as solely a reduction in serum levels of IgE and FcεRI expression on mast cells and basophils. It opens up additional explanations for asthma improvement including depression of IgE-bearing "B" cells.

Anti-IgE also has been shown to inhibit late-phase reactions and inflammatory cells, certainly a critical feature of asthma.⁹ An intriguing study by Tedeschi *et al.*¹⁰ also reviews the consistent presence of autologous antibodies in patients with "nonallergic" asthma and suggests a therapeutic effect of IgE: anti-IgE complexes in addition to decreases in tissue eosinophils, lymphocytes, and interleukin-4-positive cells. Could this be one of the explanations for anecdotal success in patients with low total IgE, so-called "intrinsic asthma"?¹⁰

Overall, most physicians and most enlightened insurance carriers are likely not to use an IgE level of 29 IU/mL as a reason for denial, although the lower the IgE level is, the more likely is denial. The author would add anecdotally that the most consistent and dramatic responses in a series of 60 asthmatic patients in clinical experience have come from the treatment patients with the lower total levels of IgE,¹¹ an observation diametrically opposed to published profiling efforts working from data and trials excluding these patients from study.¹²

WHAT ABOUT THE USE OF ANTI-IgE IN PREGNANCY?

Although it is not common clinical practice to initiate omalizumab in a pregnant asthmatic patient, it is very possible that a woman of child-bearing age, particularly those with a good clinical response, may become pregnant while receiving this long-term therapy. Most allergists have reacted by using the same principles used in specific allergy (IT) immunotherapy—to continue the treatment. Although the philosophy is parallel, there really is no knowledge as to parallel risk. Omalizumab is rated as a category B drug. There have been reports of spontaneous abortion during therapy, but no indication that it exceeds the expected rate. Birth defects associated with therapy still have not been reported.

WHAT IS THE RISK OF CANCER?

A common notion among physicians is that allergic people may be more resistant to certain forms of cancer, therefore raising the possibility of increased cancer if the IgE system was compromised. This concept of a lower cancer rate in atopy was first presented in 1977.¹³ It was followed with a comparative survey of 392 patients with three types of malignancy and 303 controls.¹⁴ The conclusion was that the patients with endodermal neoplasia (lung, gut, bladder, and prostate) had lowered forms of allergic disease. A more recent study with a larger sample size of 6913 patients with smoking, asthma, hay fever, hives, or food allergy suggested the contrary—that allergic patients had a slightly higher risk odds ratio for developing some types of malignancy.¹⁵ It is unlikely that either study had sufficient patient populations.

A detailed analysis of the available literature from clinical trial patients managed with anti-IgE is reassuring. Malignancies were noted in 20 of 4127 (0.5%) patients exposed to anti-IgE compared with 5 of 2236 (0.2%) of control patients, which on the surface might cause concern. However, a more in-depth analysis finds that the vast majority of the 20 cases occurred in an older patient population, which was not matched with controls. At least five of 20 had the same cancer before exposure to anti-IgE or were entered in the trial with existing cancer. 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 hemonchologists in preliminary analysis to suggest there is no concern for causation of malignancy by anti-IgE based on current data.

Although the surveys or initial data are not compelling in implicating a role of IgE in protecting against malignancy, such a possibility is intriguing and warrants additional studies. IgE receptor expression provides eosinophils with means to exert their antitumoral activity through IgE-mediated antibody-dependent cellular cytotoxicity. In addition, eosinophils play a role in interleukin-4 antitumor activity and Fc α R, Fc γ R1, and Fc γ R2 contribute to antitumor activity. Indeed, IgE-specific antitumor antibodies have shown promise in animal models as therapy for ovarian tumors, suggesting that IgE may be used, with manipulation, as direct anticancer defense¹⁶

Ongoing studies of the potential for cancer association include the "Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-Term Safety in Patients with Moderate-to-Severe Asthma" (Excels). This is a 5-year study seeking to compare 5000 omalizumab-treated patients with 2500 nontreated patients. The primary outcome measures will include the incidence of all malignancies excluding nonmelanoma skin carcinoma.

IS THERE A GREATER RISK OF PARASITIC INFECTIONS IN PATIENTS TREATED WITH ANTI-IgE?

Because IgE has a role in the defense against parasites, there naturally is some concern about disabling this defense mechanism—particularly in populations of people who travel to areas where parasitic infections are endemic.¹⁶ But the reduction of IgE, whether pharmaceutical or by anti-IgE monoclonal antibodies, may actually improve the disease process of parasitosis by leading to reduced worm burden and decreased egg production in schistosoma and *Paragonimus westermani*. Suppression of nonspecific IgE may allow more specific antiparasitic IgE and IgE-independent cellular tox-

icity enhanced by reduction of parasitic-specific IgE to Fc ϵ R1/CD23 on macrophages and eosinophils.^{17,18}

A more pressing issue clinically is the inadvertent use of anti-IgE treatment in cases of existing parasitosis, particularly in cases of strongyloides because of the possibility of super infection¹⁹. However, those individuals are likely to have an IgE of >1000 and are therefore not good candidates for treatment of patients under consideration for anti-IgE treatment. There is additional evidence of lack of danger from anti-IgE after an analysis of individuals in Brazil.²⁰ One hundred thirty-seven patients (68 patients with anti-IgE and 69 patients on placebo) at high risk of infection with ascariasis were observed for 1 year. The geohelminth infection rate was slightly higher in the treated group than in the placebo group. Clinically, the course, severity, and response to treatment were the same.

In clinical trials of anti-IgE in asthmatic and allergic patients, 0.19% of patients on active drug reported headlice, swimmers' itch, pinworm, scabies, or amoebiasis compared with 0.16% of placebo-treated patients. There was no difference in the intensity or duration of disease between the two groups.²¹ Despite these reassuring studies, widespread use of anti-IgE is being monitored carefully.

WHAT ARE THE IMPLICATIONS OF SKIN TESTS THAT REMAIN POSITIVE AFTER TREATMENT?

It is logical to assume that, because of careful initial and follow-up studies showing reduction in receptors and, indeed, skin tests, the clinical experience should follow.²²⁻²⁴ However, some evidence from preliminary abstracts and large numbers of anecdotal reports suggest that skin tests may remain in many asthmatic patients despite extended treatment.²⁵⁻²⁷

If skin-prick tests do remain for an extended period, either the dosage suggested for anti-IgE is inadequate or the half-life of IgE implanted on the mast cells is longer than anticipated. In the review by Soresi and Togias,¹ there is a suggestion that skin mast cells reflect those in the lungs closely. Positive skin-prick tests suggest an immune system that is armed and dangerous. Indeed, at least three cases of anaphylaxis with standard IT have been reported despite at least 6 months of pretreatment with omalizumab.²⁷ Figure 1 shows little change in the initial and 6-month follow-up prick-puncture tests for common antigens in a patient on standard IT and anti-IgE concomitantly. This patient experienced Grade III anaphylaxis within 20 minutes of an allergy injection despite 1 year of anti-IgE treatment. The potential for anaphylaxis should come as no surprise because some anaphylaxis was noted in peanut trials despite high levels of anti-IgE.²⁸ Additional, larger, and more rigorous studies of these observations are indicated.

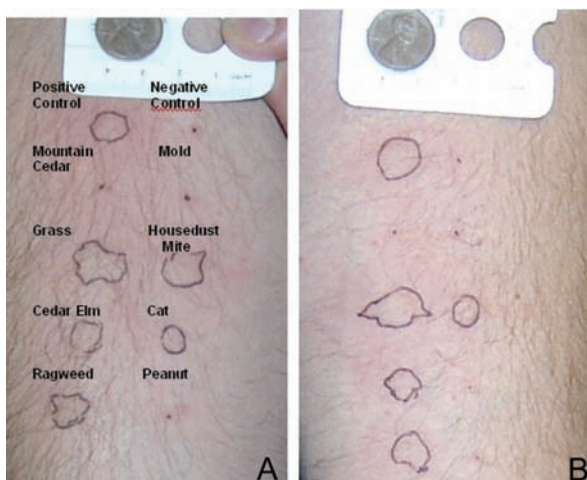


Figure 1. Skin testing on patients before and during anti-IgE therapy. (A) Baseline skin-prick puncture; (B) 6-month skin-prick puncture.

IS ANTI-IgE USEFUL IN RUSH IT OR CONCOMITANT-SPECIFIC IT?

One of the most attractive uses of anti-IgE might be its assistance in preparing sensitive patients for either rush IT, or even standard specific antigen IT. Initial trials with the combination have raised both expectations and warnings.^{29,30,33,34}

Follow-up studies, as reported in this review by Parks and Casale,³⁵ suggest that anti-IgE is helpful in reducing most of the parameters associated with anaphylaxis; however, caution is advised for physicians in interpreting these results for “off-label” use of anti-IgE as preparation for standard clinical rush because the final doses used in these studies are considerably lower than what is normally considered “maintenance” for usual rush doses. Indeed >70% of systemic reactions are encountered in standard rush (with pretreatment) in the last two doses, leading to maintenance doses as defined in practice parameters.³¹ More studies with more aggressive doses are definitely indicated.

Because IgE is tied up in a complex of IgE:IgG, another theoretical concern for IT and anti-IgE is whether injected antigen may be found by complexes of IgE:IgG. That may affect the immune system’s processing of antigen and contribute to a diminished effect. Although merely annoying with aeroallergens, the combination of insect venom and anti-IgE with less than optimal response is much more problematic.

ARE THE COMPLEXES ASSOCIATED WITH ANTI-IgE USEFUL, PROBLEMATIC, OR INCONSEQUENTIAL?

Omalizumab has two binding FAb arms for antigens. IgE has two sites for the binding by omalizumab. For the most part, the complexes formed by IgE and anti-IgE have been considered inconsequential because the complexes formed by omalizumab and IgE in the

treated patients are small, with the most common containing three omalizumab IgG and three IgE molecules. These complexes are soluble and stable, suggesting that the immune complexes do not deposit in kidneys and do not elicit antibody response in the treated patients. What is not known is whether the free FAb arms of the bound IgE can attract and bind antigen it sees in blood or tissue. Because it seems reasonable that they can, the complex actually may act as a giant floating buffer, particularly when the IgE level is initially high. To see IgE levels increase 2–10 times is not unusual, leaving many to wonder about the fate of absorbed or injected antigen. “Is that good—are these complexes therapeutic—do they prevent normal antigen processing?” Varghese *et al.* reported a decrease in wheal size immediately after injections of omalizumab and have theorized that the IgE/allergen immune complexes steatorically hinder the use of allergen and IgE on mast cells.³²

There are anomalies of complex formation. Because total IgE theoretically increases 2–10 times as commercial assays detect both free IgE and that tied up in complexes, total IgE assays are not commonly done. However, some physicians following editorial suggestions²⁵ have noticed that total IgE may not consistently increase after anti-IgE immunization.²⁸ The serum levels, baseline and after 6 months of treatment are presented for 60 patients followed in clinical patients on anti-IgE in Fig. 2. Although the average rise of total IgE is 3.5 times that of baseline, as many as 8–10% of patients may see either a decrease or a minimal rise. These findings suggest that either the complexes are being more rapidly metabolized or that lower levels of IgE are being produced, perhaps as a result of specific B-cell depression or B-cell switching. The academic hazard of using unpaired samples in national laboratories is acknowledged, and rigid analysis of IgE level using uniform labs and paired samples is suggested. Additional, larger, and well-designed trials looking for anomalies of B-cell function, complex formation and effect, total IgE levels above and below the usual recommended levels for treatment, and skin-test persistence may assist in profiling potential responders to treatment.

HOW LONG SHOULD ANTI-IgE BE USED?

Currently, there are no published studies to suggest the length of time asthmatic patients should be treated with anti-IgE. The lack of an end point is one of the major reasons that insurance carriers place so many barriers to approval. If the current mechanism of action is correct, there is no reason to expect that discontinuation of therapy would not result in reaccumulation of IgE and resumption of the disease process. Although some studies have confirmed that it may take a year for the IgE levels to fall to normal, a notable omission in our knowledge base has been follow-up of asthmatic

CA	25	281
JA	491	1304
WB	73	288
PB	40	67
AB	126	489
AQ	20	84
EC	242	1055
QA	19	30
CC	289	926
TP	26	67
TC	912	3197
DC	22	50
JC	3	8
JD	193	776
WE	215	910
SF	116	332
DF	259	340
PG	1315	515
GG	2	10
BG	41	297
BH	298	382
KR	1075	1151
WH	98	288
SH	103	1063
LH	52	93
SH	273	404
JJ	276	490
NJ	33	117
ML	102	122
DL	2080	2586
MM	53	303
TM	122	446
GM	87	185
LM	144	175
SMC	262	450
SM	834	1581
GM	106	483
KM	58	320
PN	387	913
SN	196	631
MO	102	84
SP	33	165
JP	345	347
JP	791	2059
KP	130	814
DP	249	850
BP	42	242
SR	122	292
MR	485	1759
JS	455	425
ES	75	57
SS	161	669
RS	109	150
MS	539	2405
LS	203	125
GS	125	361
ET	19	493
TT	32	133
GW	7	23
LW	12	31

ID entry 6 months
IgE IgE
IU/mL IU/mL

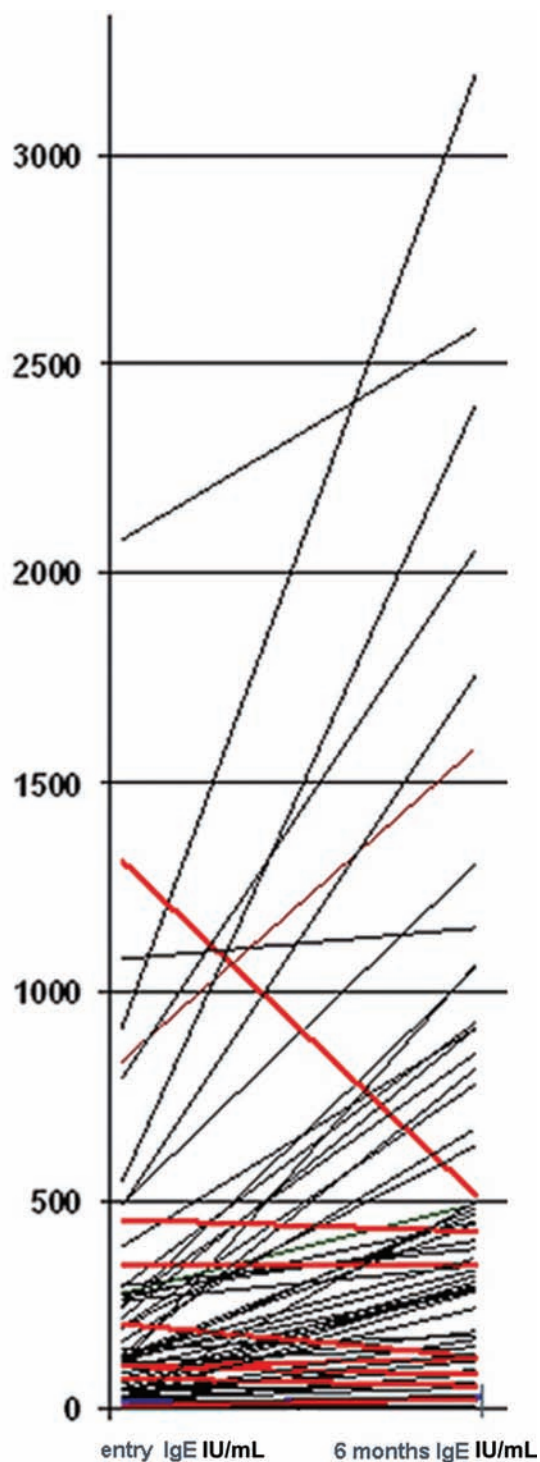


Figure 2. Left: Changes in IgE levels measured in commercial laboratories over six months of treatment with omalizumab. Right: Serum IgE levels at baseline and at 6 months (horizontal axis: IgE, IU/mL baseline 6 months).

patients treated in the longer clinical trials. Although it is a common opinion among physicians associated with clinical trials that patients may not reexacerbate to pretreatment levels, no studies or reports of clinical follow-up are seen in the medical literature. However,

increasing evidence of the more central effect of anti-IgE may give some hope to the establishment of an end point. Many physicians extrapolate customs associated with standard IT to alter both the frequency and the length of anti-IgE therapy.

HOW WILL ANTI-IgE BE MADE IN THE FUTURE—WILL IT GET LESS EXPENSIVE?

Those physicians fortunate enough to visit the manufacturing facilities for anti-IgE will see the equivalent of a top-secret space-age brewery. Anti-IgE is brewed in row after row of 15,000-liter stainless steel vats managed by workers dressed in HAZMAT suits. There is at least hope that, once research and development costs are recovered and processes are smoothed out, the large costs associated with this and other biotechnological products will decrease.

On the distant horizon is the possibility of human monoclonal antibodies being produced by transgenic animals.^{36,37} Four milligrams of monoclonal antibodies are found in each egg of transgenic chickens. Perhaps someday the incredible edible egg also may manage allergy and asthma.

REFERENCES

- Soresi S, and Togias A. Mechanisms of action of anit-immunoglobulin E therapy. *Allergy Asthma Proc* 27(Suppl): S15–S23, 2006.
- Chang TW. Developing antibodies for targeting immunoglobulin and membrane-bound immunoglobulin E. *Allergy Asthma Proc* 27(Suppl): S7–S14, 2006.
- Ledin A, Bergvall K, Hillbertz NS, et al. Generation of therapeutic antibody responses against IgE in dogs, an animal species with exceptionally high plasma IgE levels. *Vaccine* 24(1):66–74, 2005.
- Krathen RA, and Hsu S. Failure of omalizumab for treatment of severe adult atopic dermatitis. *J Am Acad Dermatol* 53:338–340, 2005.
- Ohrui T, Funayama T, Sekizawa K, et al. Effects of inhaled beclomethasone dipropionate on serum IgE levels and clinical symptoms in atopic asthma. *Clin Exp Allergy* 29:294–297, 1999.
- Zieg G, Lack G, Harbeck RJ, et al. In vivo effects of glucocorticoids on IgE production. *J Allergy Clin Immunol* 94:222–230, 1994.
- Leynadier F, Doudou O, Gaouar H, et al. Effect of omalizumab in health care workers with occupational latex allergy. *J Allergy Clin Immunol* 113:360–316, 2004.
- Leung DY, Sampson HA, Yunginger JW, et al. and Avon Longitudinal Study of Parents and Children Study Team. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 348:986–993, 2003.
- Ong YE, Menzies-Gow A, Barkans J, et al. Anti-IgE (omalizumab) inhibits late-phase reactions and inflammatory cells after repeat skin allergen challenge. *J Allergy Clin Immunol* 116:558–564, 2005.
- Tedeschi A, Comi AL, Lorini M, et al. Autologous serum skin test reactivity in patients with non-allergic asthma. *Clin Exp Allergy* 35:849–853, 2005.
- Lanier BQ. Observations of patients treated with anti-IgE over two years. Abstract European Academy of Allergology and Clinical Immunology/World Allergy Organization (EAACI/WAO), Munich, June 2005.
- Bosquet J, Wenzel S, Holgate S, et al. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. *Chest* 125:1378–1386, 2004.
- Rosenbaum JT, and Dwyer JM. The role of IgE in the immune response to neoplasia: A review. *Cancer* 39:11–20, 1977.
- Cockcroft DW, Klein GJ, Donevan RE, and Copland GM. Is there a negative correlation between malignancy and respiratory atopy? *Ann Allergy* 43:345–347, 1979.
- McWhorter WP. Allergy and the risk of cancer. *Cancer* 62:451–455, 1988.
- Dombrowicz D, Capron A, and Capron M. Expression of IgE receptors on eosinophils. In *IgE and Anti-IgE in Asthma and Allergic Disease*. Fick R, and Jardieu P (Eds). New York: Marcel Dekker, Inc., 2002.
- Hagel I, Di Prisco MC, Goldblatt J, and 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* 26:75–84, 2004.
- Rihet P, Demeure CE, and Bourgois A. Evidence for an association between human resistance to *Schistosoma mansoni* and high anti-larval IgE levels. *Eur J Immunol* 21:2679–2686, 1991.
- Neva FA. Biology and immunology of human stongyloidiasis. *J Infect Dis* 153:397–340, 1986.
- 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 2303Novartis data on file. Novartis Pharmaceuticals Corp., East Hanover, NJ
- Data on file, Genetech Corp., South San Francisco, CA
- Macglashan D, and Miura K. Loss of receptors and IgE in vivo during treatment with anti-IgE antibody. *J Allergy Clin Immunol* 114:1472–1474, 2004.
- Togias A, Corren J, Shapiro G, et al. Anti-IgE treatment reduces skin test (ST) reactivity. *J Allergy Clin Immunol* 101:S171, 1998.
- Beck LA, Marcotte GV, MacGlashan D, et al. Omalizumab-induced reductions in mast cell Fce psilon RI expression and function. *J Allergy Clin Immunol* 114:527–530, 2004.
- Lanier BQ. Unanswered questions and warnings from two years clinical experiences with omalizumab. *Allergy Asthma Proc* 26(6):453–459, 2005.
- Lanier BQ. The effect of omalizumab on Prick Puncture skin tests at six months. ACAAI 2004 (Abs).
- Lanier BQ. Case reports of three patients with anaphylaxis to grass SIT while omalizumab pre-treated for six months. Abstract EAACI/WAO Munich, June 2005.
- Leung DY, Sampson HA, Yunginger JW, et al. and Avon Longitudinal Study of Parents and Children Study Team. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 348:986–993, 2003.
- Wahn U, and Hamelmann E. Anti-IgE therapy combined with specific immunotherapy: Pro. *Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf A M* 94:269–271, 2003.
- Lanier B, and Marshall GD Jr. Unanswered questions on omalizumab (Xolair) patient selection and follow-up. *Ann Allergy Asthma Immunol* 92:198–2000, 2004.
- Harvey SM, Laurie S, Hilton K, and Khan DA. Safety of rush immunotherapy to multiple aeroallergens in an adult population. *Ann Allergy Asthma Immunol* 92:414–419, 2004.
- Varghese M, Lieberman P, Treadwell G, et al. Omalizumab reduction in skin tests and symptom scores. Abstract, ACAAI 2004.
- Larche M. Anti-IgE therapy combined with SIT: Contra. *Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf A M* 94: 272–276, 276–278, 2003.
- Hamelmann E, Rolinck-Werninghaus C, and Wahn U. Is there a role for anti-IgE in combination with specific allergen immunotherapy? *Curr Opin Allergy Clin Immunol* 3:501–510, 2003.
- Parks KW, and Casale TB. Anti-immunoglobulin E monoclonal antibody administered with immunotherapy. *Allergy Asthma Proc* 27(Suppl): S33–S36, 2006.
- Nils L. Human antibodies from transgenic animals. *Nat Biotechnol* 23:1117–1125, 2005.
- Lei J, van de Lavoie M, and Albanese J. Production of human monoclonal antibody in eggs of chimeric chickens. *Nat Biotechnol* 23:1159–1109, 2005. □

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.