

# Anti-IgE Therapy for Allergic Asthma and Other Allergic Diseases

**Bob Q. Lanier and Tse Wen Chang**

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The recent introduction of a radically new commercial product designed to target the central mediator of type I hypersensitivity reactions has spurred renewed interest in the roles of IgE in asthma and other allergic diseases. Theoretically, if an anti-IgE antibody can completely neutralize the key mediator, then allergy could be clinically eliminated. Clinical trials on anti-IgE do not completely support this view, however. These preliminary efforts to cripple IgE have resulted in a greater appreciation of the complexity and redundancy of the human immune system.

## Background

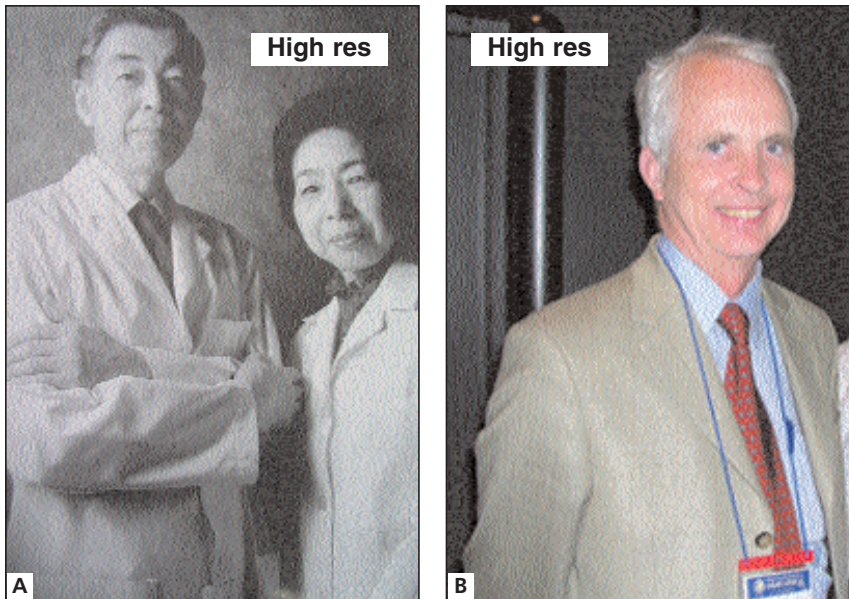


Figure 27-1.

Shortly after the discovery of IgE in 1968 by Ishizaka and Ishizaka (A) and Johansson (B), native IgG with binding specificity for IgE (anti-IgE) was found in the blood of many normal subjects and allergic patients. Initial hopes of selective stimulation to elicit a beneficial specific autoimmune response against IgE never came to fruition, leaving the scientific community to experiment with synthetic peptide alternatives. In 1987, Chang proposed a therapeutic approach based on the development of monoclonal anti-IgE antibodies that have a unique set of binding specificities. Such a therapeutic antibody would have the ability to neutralize or “tie up” IgE and downregulate the synthesis of IgE, and would be suitable and safe for long-term *in vivo* use in patients. In more than 15 phase II and III trials, anti-IgE has also been shown to be safe and efficacious for treating allergic asthma, allergic rhinitis, peanut allergy, and allergy to latex. In 2002, Australia became the first country to approve this humanized anti-IgE antibody, called omalizumab. In June 2003, the US Food and Drug Administration approved omalizumab for treating adult and adolescent patients with moderate to severe asthma, thus launching a new and unique approach to the management of allergic diseases. As the first biologic therapeutic agent for asthma, anti-IgE has several immunoregulatory pharmacologic effects—thus making it the first immunoregulatory agent for allergic diseases since Noon introduced desensitization immunotherapy in 1911.

The mammal immune system has evolved into a highly redundant bodily system, with many overlapping immune mechanisms targeting the same invading pathogenic organisms. IgE is an important immune component against the invasion of parasites, particularly helminths, against which a strident IgE response in humans is commonly seen. However, mice whose IgE production is entirely abolished by immunological or genetic manipula-

tion can mount an effective immune defense against challenges of nearly all types of pathogenic organisms, including parasites. In people living in many regions of the world, IgE is probably dispensable, because some healthy, immunologically normal people do not have detectable IgE in their blood. However, the reactivity of the immune system with foreign and yet innocuous protein associated with airborne pollen, animal dander, in molds, or in food induces the production of IgE-specific antibodies against such benign proteins, leading to the development of various types of diseases and conditions associated with IgE-mediated allergy. Most of the IgE produced does not seem to have a known specific assignment or activity. In most patients, only a small proportion of the total IgE is specific for the allergens to which the patients are sensitized. The anti-IgE agent omalizumab targets the entire IgE class and, therefore, relatively large doses are required for treating patients. However, unlike allergen-specific immunotherapy, omalizumab is effective for patients regardless of their allergens.

The clinical symptoms of allergy result from the discharge by mast cells and basophils of histamine, leukotrienes, tryptases, and many other pharmacologic mediators from the densely packed granules inside those cells. This process is initiated by the selective binding of allergenic protein molecules to IgE already bound by the high-affinity IgE receptors (FcεR1; see later) on the surface of those cells, leading to the cross-linking of the bound IgE and the subsequent aggregation of the underlying FcεR1, which then trigger the cells almost instantly to release the contents of the cytoplasmic granules through exocytosis. (A, *courtesy of William Coupon, NIH monograph *Breath of Life**; B *courtesy of Bob Q. Lanier, MD*).

## Biology

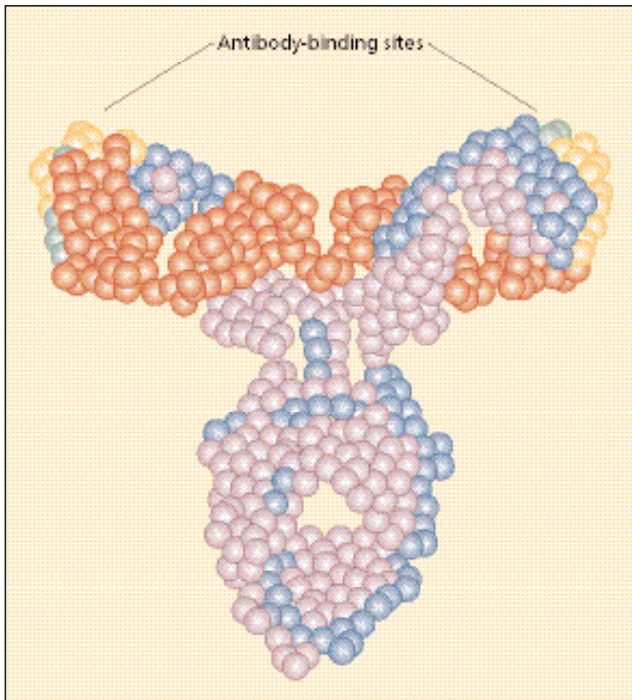


Figure 27-2.

Antibody-binding sites. Commercial anti-IgE, omalizumab, is a recombinant DNA–derived humanized monoclonal antibody with an IgG4 kappa framework. Heavy and light chains are made up by retaining the complementarity-determining regions (CDRs) of the heavy and light chains of the parental murine antibody and replacing nearly all the variable-region framework segments and all constant domains of heavy and light chains with appropriate corresponding parts of human heavy and light chains. The CDRs, which represent less than 5% of the total sequence, are hypervariable among antibodies and unique for each antibody. These segments form the antigen-binding sites.

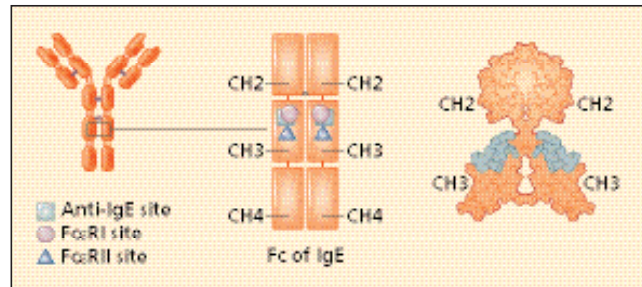


Figure 27-3.

In *in vitro* culture, an ordinary antibody against IgE has been shown to be a more potent inducer than an allergen in stimulating mast cells and basophils to discharge their pharmacologic mediators. Such an anti-IgE antibody would probably invariably cause anaphylactic reactions and shock were it injected into a human subject. An anti-IgE therapeutic, such as omalizumab, differs from an ordinary anti-IgE therapeutic in that it has a unique set of binding specificities. Such binding specificities reside in a region on the CH3 domain of the E heavy chain of IgE, near the junctions of CH2 and CH3 domains. The binding sites on IgE for the high-affinity IgE receptor overlap that for anti-IgE. FcεRI receptors are expressed on mast cells, basophils, and activated neutrophils. FcεRII receptors (low-affinity IgE receptors) are expressed on B cells and granulocytes. Anti-IgE cannot bind to IgE that is already bound by FcεRI or FcεRII.

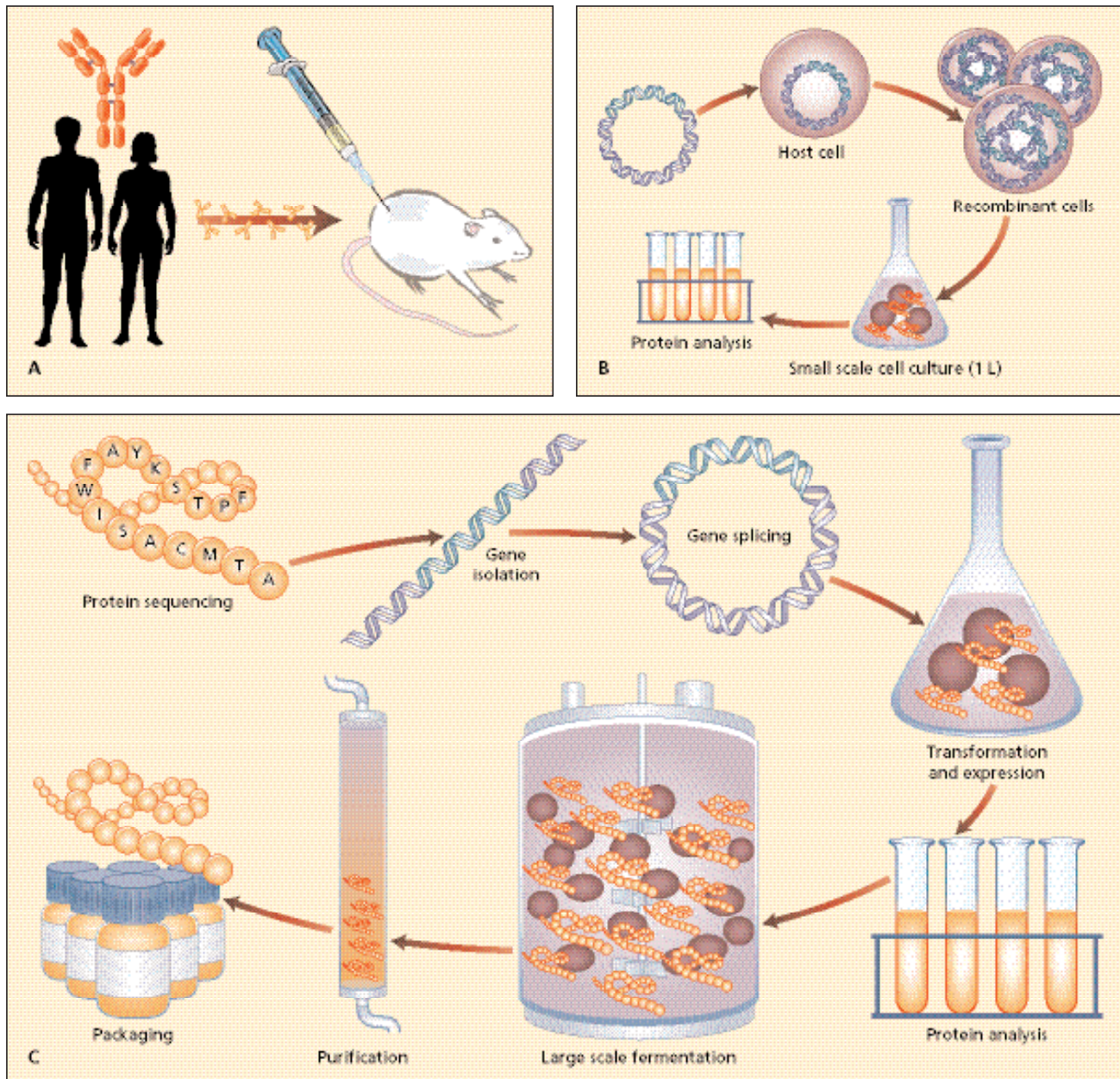


Figure 27-4.

Antibody production. **A**, Mice are hyperimmunized with human IgE. Their spleen cells, containing B lymphoblasts with reactivity to human IgE, are then fused with cells of a mouse myeloma cell line, yielding hybrids that could survive and grow in a medium provided with certain selective drugs. The thousands of hybridoma clones are allowed to grow individually (by limiting dilution) in tiny culture wells.

**B**, The antibodies secreted by the clones are then screened sequentially for their binding specificities (whether they bind to human IgE and mouse IgE-expressing B cells strongly and thus are incapable of stimulating basophils from very allergic donors). The hybrids that secreted antibodies with the unique set of binding specificities are then kept and expanded for the next steps of process.

**C**, "Antibody engineering" cleaves all but the antigen-binding sites of the mouse antibody. The gene segments encoding the  $V_H$  and  $V_L$  domains of the antibodies secreted by the selected hybridoma

clones are then cloned. The three complementarity-determining regions (CDRs) in each  $V_H$  and  $V_L$  domain, which constitute the antigen-binding sites, are then identified by comparative analysis of hundreds of  $V_H$  and  $V_L$  sequences in the database and known CDRs of other antibodies.

Completed recombinant heavy and light chain genes are then inserted into appropriate expression plasmid cassettes. The completed cassettes are transfected into a Chinese Hamster Ovary (CHO) cell line host for expressing the introduced recombinant antibody genes. The selected CHO clones that secreted humanized antibody with the desired binding affinity for human IgE at attractive yields are then adapted to grow in suspension in large bioreactor tanks. Currently, the commercial anti-IgE antibody product is manufactured in a plant using bioreactor tanks that are 12,000 liters in size.

## The Paradox of Increasing IgE

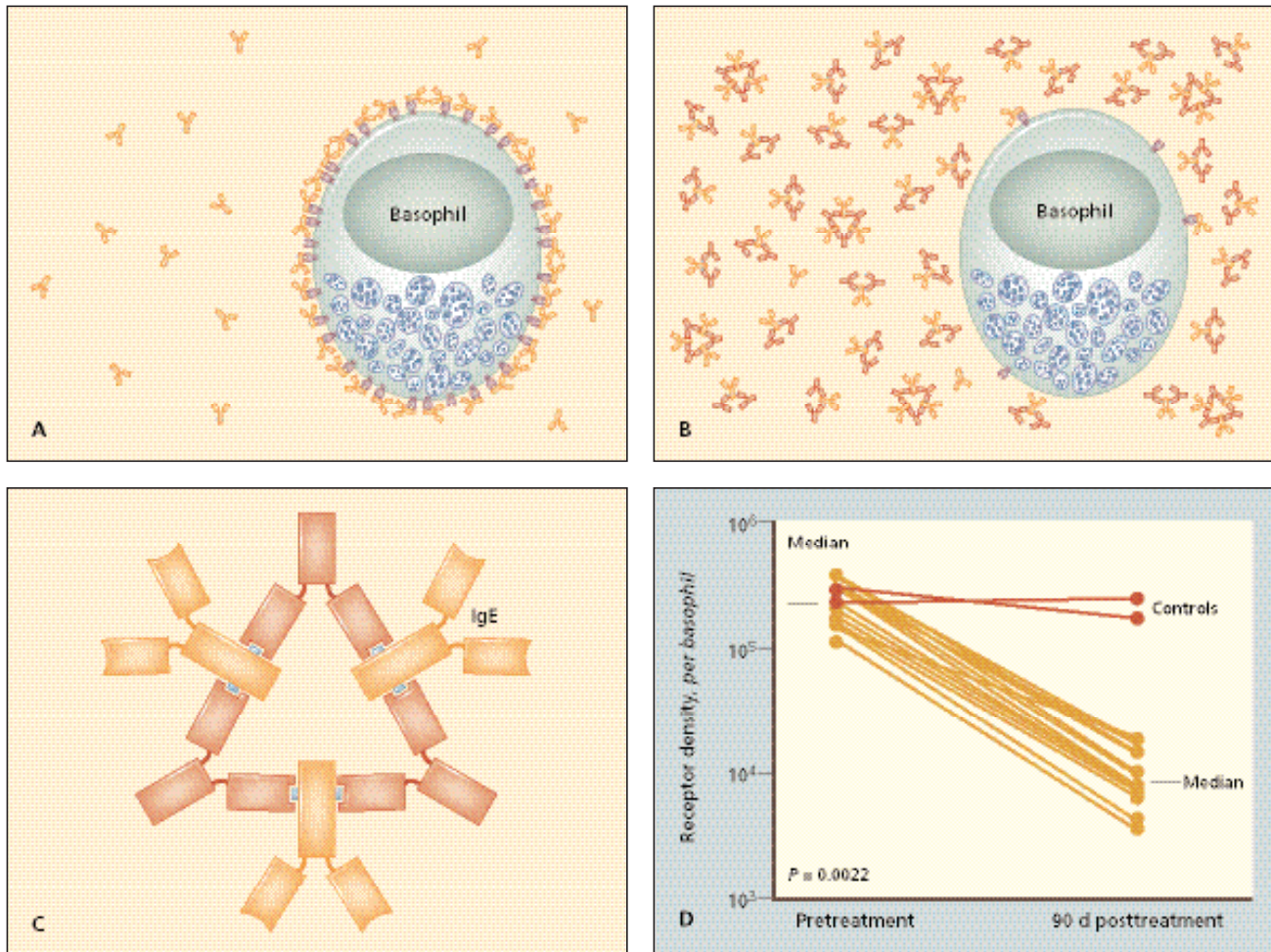


Figure 27-5.

How antibodies tie up IgE. **A**, When injected subcutaneously, anti-IgE diffuses into the bloodstream and is active almost immediately; maximum serum concentrations occur in 7 to 8 days, with an absolute bioavailability of 62. **B**, As free IgE drops beginning at 1 hour, total IgE (bound plus free IgE) rises because the complexes clear at a much slower rate than the antibody by itself.

**C**, IgE and anti-IgE form complexes of, for the most part, trimers. Physicians may find that the total IgE (and results of

radioallergosorbent tests, which measure individual clones) may rise as much as five times.

**D**, Expression of high-affinity IgE receptors on peripheral blood basophils from 15 subjects before and after 90 days of treatment with omalizumab. As free IgE levels fall, the number of receptors drops (downregulate). The farther apart the receptors are, the less likely that bridging of antibody occurs, and degranulation results. (D adapted from McGlashan *et al.* [1]).

## Benefits of Anti-IgE Therapy

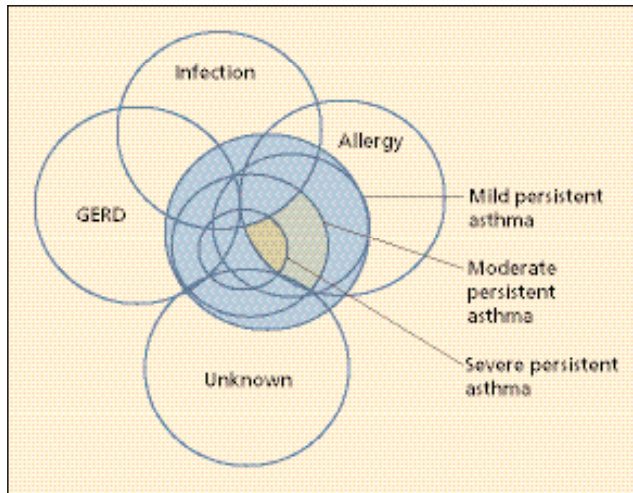


Figure 27-6.

Various factors in asthma. It seems obvious that people with IgE-mediated disease will benefit from anti-IgE therapy. However, the practical application of the drug is much more complicated: because the current indication is moderate to severe asthma, the choice of candidates becomes more difficult. Although theoretically the drug is more likely to provide effects even in mild asthma, its approval indication suggests the need to analyze asthma in a much different way than is customary. The asthmatic patient whose lung process is primarily allergic has the greatest chance of ideal response. Anti-IgE therapy is also being studied in food allergy, rhinitis, urticaria, latex sensitivity, polyposis, and even nonatopic conditions. GERD—gastrointestinal reflux disease.

## Drug Dosing

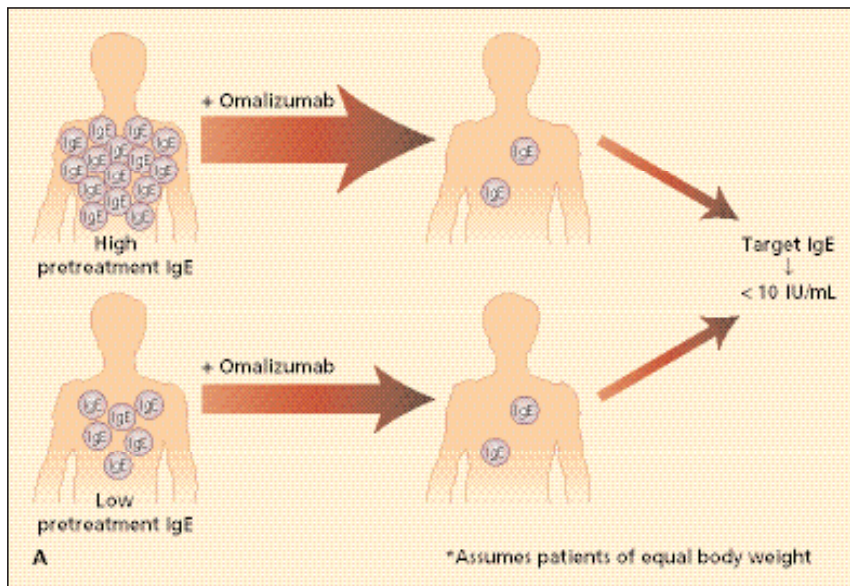


Figure 27-7.

Considerations in drug dosing. A, To downregulate the receptors on the mast cells, it is necessary to reduce the IgE level substantially, using such variables as the patient's weight and baseline IgE level. Clinical improvements occur when free IgE levels in serum are reduced to 50 ng/mL (20.8 IU/mL) or less.

(Continued on next page)

		Weight, kg							
		20-30	> 30-40	> 40-50	> 50-60	> 60-70	> 70-80	> 80-90	> 90-150
Baseline IgE, U/ml	> 30-100	150	150	150	150	150	150	150	300
	> 100-200	150	150	300	300	300	300	300	450
	> 200-300	150	300	300	300	450	450	450	600
	> 300-400	300	300	450	450	450	600	600	
	> 400-500	300	450	450	600	600	750	750	
	> 500-600	300	450	600	600	750			
	> 600-700	450	450	600	750				
	> 700-800	450	600	750					
	> 800-900	450	600	750					
	> 900-1000	600	750						
	> 1000-1100	600	750						
	> 1100-1200	600							
	> 1200-1300	750							

Figure 27-7. (Continued)

**B**, Dosage table. This dosage table was developed resulting in 150 to 375 mg by subcutaneous injection every 2 or 4 weeks. This dosage table factors weight and IgE levels to compute the number of milligrams to be given by subcutaneous injection every 2 or 4 weeks. Vials contain 150 mg (*ie*, the brown colors indicate 1 vial, blue colors indicate 2 vials, yellow colors indicate 3 vials, purple colors indicate 5 vials, and green colors indicate 6 vials). For example, a person weighing between 90–150 kg with a baseline IgE of 30–100 would get two vials per month (either two vials per month or one vial every 2 weeks).

## Safety

### Safety Concerns Regarding Anti-IgE Therapy

Adverse events reported in < 3%

Fever, arthralgia, rash, urticaria, pruritus, dermatitis, flu-like symptoms: 1%–7%

Anaphylactoid/anaphylaxis reaction in seven patients

Malignancies in 0.5%

Figure 27-8.

Safety concerns. Adverse events were reported in less than 3% of patients (Product insert, Xolair: Genentech, Inc. and Novartis Pharmaceuticals, East Hanover, NJ). Because complexes are formed, adverse events of fever, arthralgia, rash, urticaria, pruritus,

dermatitis, and influenza-like symptoms received special attention and were reported in 1% to 7% of all omalizumab-treated patients (similar to the placebo group). Three treated patients were reported to have a systemic reaction described as anaphylactoid/anaphylaxis, but were delayed from 90 to 120 minutes. Malignancies were seen in 20 of 4127 (0.5%) anti-IgE-treated patients versus five of 2236 (0.2%) control patients. There was no pattern to the malignancies, with breast, nonmelanoma skin, prostate, melanoma, and parotid occurring more than once, and five other types occurring once each. A number of the malignancies were recurrences of previously existing cancer, and several patients with cancer were enrolled. Although omalizumab has been designated category B in pregnancy, IgG molecules of which it is constructed are known to cross the placental barrier. There are no adequate and well-controlled studies of omalizumab in pregnant women or in human milk.

## Questions Regarding Anti-IgE Therapy

## Questions

Why is the improvement in major clinical trials with asthma so modest on average?

Because IgE is thought to be important in cancer defense, and because trials show more cancer in treated patients than controls, is there a legitimate concern in weakening this defense system?

Because IgE is important in parasitic defense, will anti-IgE therapy be hazardous for travelers or for people living in parasitically endemic areas?

Current use of this treatment is restricted to patients with an IgE level between 30 and 700 IU; could it be effective outside those ranges?

## Answers

There is a need for a new approach to moderate to severe persistent asthma not controlled with inhaled steroids. However, asthma meeting these criteria is not automatically allergically invoked. The mere presence of a defined allergen in an asthmatic patient may or may not be relevant. Hence, a modification of the standard criteria for consideration of implementation is offered: anti-IgE should be considered in moderate to severe persistent asthma when concomitant allergy seems important in the causation or provocation of the asthmatic process.

Although commonly cited by clinicians, there is little if any evidence that allergic patients have any advantage over nonallergic patients regarding the incidence or severity of cancer. Hence there is little possibility that inhibiting the antibodies and downregulating receptors on mast cells and basophils should render a patient more susceptible to cancer. The only way to truly answer this question is through long-term observations with specific endpoints on neoplasia. These studies are underway.

Animal trials inhibiting IgE have not shown detrimental responses. In one Brazilian trial, individuals on anti-IgE were reinfected with ascariasis and not found to have more pronounced disease. Doubt still exists about whether activity against other parasites might remain.

The 30- to 700-IU range currently in the dosing chart reflects the statistical risk of asthma in an allergic person, but does not define the state or severity of allergy. Clearly, individuals with lower levels of IgE may have severe, even anaphylactic allergy; conversely, individuals with IgE levels higher than 700 may have no discernable clinical allergy.

Figure 27-9.

Questions about anti-IgE therapy.

## Reference

1. McGlashan DW Jr, Bochner BS, Adelman DC, *et al.*: Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol* 1997, 158:1438–1445.

## Recommended Reading

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