# Omalizumab

**Omalizumab**, sold under the trade name **Xolair**, is a humanized antibody originally designed to reduce sensitivity to inhaled or ingested allergens, especially in the control of moderate to severe allergic asthma, which does not respond to high doses of corticosteroids. It has been approved for treating adult and adolescent patients 12 years and older with severe or moderate to severe allergic asthma in more than 90 countries, since its first of such approval in 2002 in Australia. Omalizumab was approved in March 2014 in the European Union and the U.S.A. and in about 10 other countries for treating patients 12 years and above with chronic spontaneous urticaria (CSU) (also referred to as chronic idiopathic urticaria or CIU), which cannot be treated with H1-antihistamines. CSU is not an allergic disease. Presently, the drug is being actively studied in clinical trials for various allergic diseases and some non-allergic diseases, especially skin diseases.

Omalizumab is a recombinant DNA-derived humanized IgG1k monoclonal antibody that specifically binds to free human immunoglobulin E (IgE) in the blood and interstitial fluid and to membrane-bound form of IgE (mIgE) on the surface of mIgE-expressing B lymphocytes.[1] Unlike an ordinary anti-IgE antibody, it does not bind to IgE that is already bound by the high affinity IgE receptor (FcεRI) on the surface of mast cells, basophils, and antigen-presenting dendritic cells.[2]

IgE is commonly involved in type I hypersensitivity, which manifests in the most common allergic diseases. It has been estimated that as high as 20 to 40% of the populations who live a western lifestyle in economically advanced countries are affected by allergy and seek medical help.[3] In the U.S., 8% of adults and 10% of children have asthma.[4] Allergy occurs more frequently in individuals with higher serum IgE levels, though some allergic individuals have very low serum IgE, and some people with very high IgE have no allergic problems.[2]

## 1 Medical uses

### 1.1 Allergic asthma

Omalizumab received approval by the U.S. Food and Drug Administration (FDA) in 2003 for treating patients 12 years and older with moderate to severe allergic asthma.[5] It has also received approval in many other countries for treating patients 12 years and older with severe, persistent allergic asthma. Omalizumab was approved by the European Union in 2009 for treating patients 6 to 12 years old with severe, persistent allergic asthma. Thus, its primary use is for patients mostly with severe, persistent allergic asthma, uncontrollable with oral or injectable corticosteroids.[6] Those patients have already failed step I to step IV treatments and are in step V of treatment. Such a treatment scheme is consistent with the widely adopted guidelines for the management and prevention of asthma, issued by Global Initiative of Asthma (GINA), which was a medical guidelines organization launched in 1993 in collaboration with the National Heart, Lung, and Blood Institute, National Institutes of Health, USA, and the World Health Organization.[7] The efficacy is more evident among severe asthmatics than among those with moderately severe disease. The response rates among treated severe "allergic" asthma patients are 60-80% or higher, probably depending on the patient screening procedures used by the various clinical groups of different specialties. In real-life clinical practice of 142 and 195 patients in Italy and Germany, respectively, 77 to 79% of patients or physicians gave a response of "excellent or good" for GETE (global evaluation of treatment effectiveness) scale after being treated with omalizumab for four months.[8][9] Because 20 to 30% of adult asthma cases are not related to allergy,[9] a reliable way to identify treatable patients has been a subject of considerable research interest.[10][11] The primary benefits for the responding patients are reduced numbers of exacerbations, improved lung function, reduced numbers of emergency visits to the doctors, reduced days of hospitalization, and increased quality of life measurements.[8][9] The other major benefit is that most responding patients can reduce or spare entirely the use of corticosteroids, which cause multiple serious side effects, when used at high doses for extended periods.[12]

Due to the requirement for long-term administration and hence the high cost of an omalizumab treatment regimen, and to the concern over long-term safety, treatment is not yet very common, especially in developing countries where medical funds are relatively scarce. Another barrier to wide use is its injectable dosage form, which requires the patient to visit a physician's office or clinic every 2 to 4 weeks during treatment. In August 2010, the National Institute for Clinical Excellence (NICE) in the United Kingdom ruled that omalizumab should not be prescribed on the National Health Service (NHS) to children under 12, causing widespread condemnation from asthma charities.[13] NICE concluded that the high costs of the compound, over £250 per vial, did not represent a sufficiently high increase in quality of life. However, on March 7, 2013, NICE issued "final draft guidance" about

the allowance of omalizumab. It recommended the drug as an option for treating severe, persistent allergic asthma in adults, adolescents and children following additional analyses and submission of a patient access scheme (PAS) by Novartis, the manufacturer.[14] Some immunologists have also suggested that because IgE may be a natural defense against parasitic diseases, treatment should not be recommended when living in environments where the presence of parasites is common.

### 1.2 Chronic spontaneous urticaria

Xolair was approved in March 2014 in the European Union and the U.S.A. and in about 10 other countries for treating patients 12 years and above with chronic spontaneous urticaria (also called chronic idiopathic urticaria), which cannot be treated with elevated doses of H1-antihistamines.

Chronic urticaria affect about 0.5 to 1% of the world population and among those patients, two thirds have CSU, and among them, about half cannot be adequately treated even with high doses (4 times regular doses) of H1-antihistamines.[15][16] Since CSU is not an allergic disease and does not obviously involve IgE, how omalizumab effectively treats CSU is currently a hotly pursued research subject. The serum concentrations of IgE in CSU patients are generally much lower than those in patients with allergic asthma.

## 2 Adverse effects

The main adverse effect is anaphylaxis (a life-threatening systemic allergic reaction), with a rate of occurrence of 1 to 2 patients per 1,000.[6][17] Like other protein and antibody drugs, omalizumab also causes anaphylaxis, although at a relatively low frequency among antibody drugs. The allergic reaction is probably not due to the binding characteristics of the antibody drug, but to the protein nature of the antibody. The patients who use omalizumab are generally highly allergic. Thus, even though the drug is administered with the purpose to suppress allergy (including anaphylactic reactions), it does not work immediately after injection.

It also increases the risk of strokes and heart disease by a small amount.[18]

IgE may play an important role in the immune system's recognition of cancer cells.[19] Therefore, indiscriminate blocking of IgE-receptor interaction with omalizumab may have unforeseen risks. The data pooled in 2003 from the earlier phase I to phase III clinical trials showed a numeric imbalance in malignancies arising in omalizumab recipients (0.5%) compared with control subjects (0.2%).[6] To clarify this imbalance, a more recent study was performed based on pooled analysis using much more comprehensive data from 67 phase I to IV clinical trials. The prespecified primary analysis assessed the incidence of primary malignancy in 32 randomized, double-blind, placebo-controlled (RDBPC) trials. In this analysis, there were 11,459 unique patients in all clinical trials (7,789 received omalizumab). The primary analysis identified malignancies in 25 patients (RDBPC trials): 14 in 4,254 omalizumab-treated patients and 11 in 3,178 placebo-treated patients. Incidence rates per 1,000 patient-years of observation time for omalizumab- and placebo-treated patients were 4.14 (95% CI, 2.26-6.94) and 4.45 (95% CI, 2.22-7.94), respectively; the corresponding rate ratio was 0.93 (95% CI, 0.39-2.27). Primary malignancies were of varying histologic type and occurred in a number of different organ systems; no cluster of histologies was identified. The study thus concluded that in this pooled analysis no association was observed between omalizumab treatment and risk of malignancy in RDBPC trials; the rate ratio was below unity. The data suggest that a causal relationship between omalizumab therapy and malignancy is unlikely.[20]

Concerns were raised earlier about possible induction of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), a rare form of systemic vasculitis associated with asthma, in patients receiving the drug.[21] A retrospective review, which identified and analyzed cases of Churg-Strauss syndrome using the Novartis Argus global drug safety database for omalizumab in asthma patients, has indicated that Churg-Strauss syndrome may develop in patients who have an underlying eosinophilic disorder that is unmasked by the withdrawal of corticosteroids, which is common among patients receiving this treatment.[22]

## 3 Mechanism of action

Persons with allergy are sensitized to make immune response to several or many proteins contained in one or more of the hundreds of harmless environmental substances, which they take in by inhalation (e.g., house dust mites, pollens, molds, pet animal dander, and other airborne allergens) and ingestion (e.g., wheat (gluten), peanuts, nuts, shellfish, and other food allergens), or through the skin (e.g., bee and fire ant stings, latex gloves). In these individuals, the IgE molecules, both allergen-specific and allergen-nonspecific ones, in their bodies bind to the high affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Under certain conditions, including but not limited to when the allergenic substances are taken in by a sensitized individual at substantial amounts, the allergenic proteins bind to the allergen-specific IgE bound by FcεRI on the surface of mast cells and basophils and trigger the activation of those inflammatory cells, which release a host of pharmacological mediators, such as histamine, leukotrienes, tryptase, inflammatory cytokines, and others, causing various allergic symptoms/diseases.

The rationale for designing the anti-IgE therapeutic antibodies and the pharmacological mechanisms of anti-IgE therapy have been summarized in review articles by the inventor of the anti-IgE therapy, Tse Wen Chang, and his colleagues.[2][23][24] Omalizumab inhibits the binding of IgE to FcεRI on mast cells and basophils by binding to an antigenic epitope on IgE that overlaps with the site to which FcεRI binds. This feature is critical to its pharmacological effects because a typical anti-IgE antibody can cross-link cell surface FcεRI-bound IgE, thereby aggregate FcεRI, and activate mast cells and basophils to discharge the horde of chemical mediators stored in the densely packed sacs inside the cells. However, when IgE is bound to the receptor, the antigenic epitope on IgE to which omalizumab binds is sterically hindered by the receptor and is not accessible to omalizumab binding, thus averting the anaphylactic effects presumably unavoidable with an ordinary anti-IgE antibody . Furthermore, although the peptide elements on IgE involved in binding to low affinity IgE receptor (FcεRII) on many cell types are different from the peptide elements involved in binding to FcεRI, omalizumab, by steric hindrance, also prevents binding of IgE to FcεRII. The reduced binding of IgE to both FcεRI and FcεRII has profound effects on the attenuation of IgE-mediated allergic responses.

Perhaps the most dramatic effect, which was not foreseen at the time when the anti-IgE therapy was designed and which was discovered during the clinical trials, is that as the free IgE in patients is depleted by omalizumab, the FcεRI receptors on basophils, mast cells, and dendritic cells are gradually down-regulated with somewhat different kinetics, rendering those cells much less sensitive to the stimulation by allergens.[25][26][27] Thus, in this regard, therapeutic anti-IgE antibodies represent a new class of potent mast cell stabilizers,[24] providing the fundamental mechanism for omalizumab's effects on various allergic and non-allergic diseases involving mast cell degranulation. Many investigators have identified or elucidated a host of pharmacological effects, which help bring down the inflammatory status in the omalizumab-treated patients.[28][29][30]

## 3.1 IgE in allergic diseases

Corticosteroids of various chemical structures and formulations, which offer various desired potency and pharmacokinetics and which generally effectively suppress inflammatory processes systemically or locally, have been the mainstay of medicine to treat the severe cases of various allergic diseases. Before the introduction of omalizumab, moderate to severe cases of asthma, regardless of their allergic or non-allergic nature, had been generally treated with corticosteroids and bronchodilators. Clinicians had not had persuasive reasons to dissect the role of IgE, or more precisely, its relative importance among various immune factors and pharmacological mediators, in the pathogenesis of asthma and various other allergic diseases and conditions. The availability of omalizumab as a drug to intervene the IgE pathway has provided many clinical researchers the opportunities to examine the role of IgE in various allergic diseases and, in some cases, diseases that are not obviously considered as allergic diseases.

In conjunction with achieving the practical goal to investigate the applicability of the anti-IgE therapy as a potential treatment for allergic diseases, the many corporate-sponsored clinical trials of TNX-901 and omalizumab on asthma, allergic rhinitis, peanut allergy, chronic idiopathic urticaria, atopic dermatitis, and other allergic diseases, have helped define the role of IgE in the pathogenesis of these prevalent allergic diseases. For example, the clinical trial results of omalizumab on asthma have unambiguously settled the long debate whether IgE plays a central role in the pathogenesis of asthma.[29]The availability of the drug as a treatment option for patients with severe, persistent allergic asthma has gradually persuaded the physicians treating severe asthma patients to determine whether their asthma is allergic or non-allergic in nature.

Numerous investigator-initiated case studies or small-scale pilot studies of omalizumab have been performed on various allergic diseases and several non-allergic diseases, especially inflammatory skin diseases. These diseases include atopic dermatitis, various subtypes of physical urticaria (solar, cold-induced, local heat-induced, or delayed pressure-induced), and a spectrum of relatively less prevalent allergic or non-allergic diseases or conditions, such as allergic bronchopulmonary aspergillosis,[31] cutaneous or systemic mastocytosis, bee venom sensitivity (anaphylaxis),[32] idiopathic anaphylaxis, eosinophil-associated gastrointestinal disorder, bullous pemphigoid,[33] interstitial cystitis,[34] nasal polyps, and idiopathic angiodema,.[35] The generally positive results have suggested that IgE possibly plays a key role, either directly or indirectly, in these diseases and, therefore, intervening the IgE pathway may be an effective therapeutic strategy. The results of some of these case studies and pilot studies have subsequently persuaded the drug companies marketing omalizumab to carry out larger-scale trials on some of the diseases.

## 3.2 Roles in non-allergic diseases

Several groups have reported clinical trial results that omalizumab may be effective in patients with non-allergic asthma.[36] This seems to be contrary to the general understanding of the pharmacological mechanisms of the anti-IgE therapy discussed above.[37] Furthermore, among the diseases in which omalizumab has been studied for efficacy and safety, some are not allergic diseases, because hypersensitivity reactions toward external antigens is not involved. For example, a portion of the cases of chronic idiopathic urticaria[38][39] and all cases of bullous pemphigoid[33] are clearly autoimmune diseases. For

the remaining cases of chronic idiopathic urticaria and those of the different subtypes of physical urticaria, the internal abnormalities leading to the disease manifestation have not been identified. Notwithstanding these developments, it is apparent that many of those diseases involve inflammatory reactions in the skin and the activation of mast cells. An increasing series of papers have shown that IgE potentiates the activities of mast cells[40] and omalizumab can function as a mast cell-stabilizing agent,[24] rendering these inflammatory cells to be less active.

# 4 History

Tanox, a biopharmaceutical company based in Houston, Texas, started the anti-IgE program, created antibody drug candidates, and filed its first patent application on the anti-IgE therapeutic approach in 1987.[41] In the next year, the company converted one candidate antibody to a chimeric antibody (which was later named CGP51901 and further developed into a humanized antibody, TNX-901 or talizumab). The anti-IgE therapeutic concept was not well received in the early period of the program. In order to seek funding for the anti-IgE program, the two scientist founders of Tanox, Nancy T. Chang and Tse Wen Chang, visited about 25 pharmaceutical and larger biotech companies in the U.S., Canada, Europe, Japan, and other countries to discuss collaboration throughout 1989. Representatives of Ciba-Geigy (which merged with Sandoz to form Novartis in 1996) thought the anti-IgE program scientifically interesting and executives from Tanox and Ciba-Geigy signed a collaborative agreement in 1990 to develop the anti-IgE program.[41][42]

In 1991, after several rounds of pre-IND ("investigational new drug") meetings with officials/scientists of the FDA, the FDA finally gave a nod for CGP51901 to be tested in human subjects. This approval of IND for an anti-IgE antibody for the first time was regarded a brave demonstration of professionalism for both the FDA officials and the Tanox/Ciba-Geigy team. The scientists participating in the pre-IND discussion comprehended that an ordinary anti-IgE antibody (i.e., one without the set of binding specificity of CGP51901) would invariably activate mast cells and basophils and cause anaphylactic shocks and probably deaths among injected persons. Notwithstanding this concern, they came to the same view that based on the presented scientific data, CGP51901 should have an absolutely required clean distinction from an ordinary anti-IgE antibody in this regard.[43][44] In 1991-1993, researchers from Ciba-Geigy and Tanox and a leading clinical research group (headed by Stephen Holgate) in the asthma/allergy field ran a successful Phase I human clinical trial of CGP51901 in Southampton, England and showed that the tested antibody is safe.[45] In 1994-1995, the Tanox/Ciba-Geigy team conducted a Phase II trial of CGP51901 in patients with severe allergic rhinitis in Texas and showed that CGP51901 is safe and efficacious in relieving allergic symptoms.[46]

While the Tanox/Ciba-Geigy anti-IgE program was gaining momentum, Genentech announced in 1993 that it also had an anti-IgE program for developing antibody therapeutics for asthma and other allergic diseases. Scientists in Genentech had made a mouse anti-IgE monoclonal antibody with the binding specificity similar to that of CGP51901 and subsequently humanized the antibody (the antibody was later named "omalizumab").[47] This caused great concerns in Tanox, because it had disclosed its anti-IgE technology and sent its anti-IgE antibody candidate, which was to become CGP51901 and TNX-901, to Genentech in 1989 for the latter to evaluate for the purpose of considering establishing a corporate partnership.[48] Having failed to receive reconciliation from Genentech, Tanox filed a lawsuit against Genentech for trade secret violation.[48] Coincidentally, Tanox started to receive major patents for its anti-IgE invention from the European Union and from the U.S. in 1995.[49] After a 3-year legal entanglement, Genentech and Tanox settled their lawsuits out-of-court and Tanox, Novartis, and Genentech formed a tripartite partnership to jointly develop the anti-IgE program in 1996.[50] Omalizumab became the drug of choice for further development, because it had a better developed manufacturing process than TNX-901.[50] A large number of corporate-sponsored clinical trials and physician-initiated case series studies on omalizumab have been planned and performed since 1996 and a large number of research reports, especially those of clinical trial results, have been published since around 2000, as described and referenced in other sections of this article. In 2007, Genetech bought Tanox at $20/share for approximately $900 Million.[51][52]

# 5 Dosing and administration

Omalizumab is administered subcutaneously once every 2 or 4 weeks. For each patient, the dosing schedule (2 *vs* 4 weeks between injections; and the amount of omalizumab, in milligrams, for each injection) is determined according to the serum IgE level and the body weight of the patient.[53] The underlying rationale is that the IgE present at the time of the first injection and produced during the intervals of successive injections must all be neutralized by omalizumab. The product label of Xolair initially approved by FDA covers patients with serum IgE in the range of 30 to about 700 IU/ml (international units per mililiter).[54] A clinical development effort is on-going to expand the coverage of patients with serum IgE up to 1500 IU/ml.[55]

As of May 10, 2008, the company began requiring that the drug be administered by a patient's health care provider, due to a risk of anaphylaxis. Previously, the


*Xolair (omalizumab) package with powder and solvent phials*

drug could be self-administered.

Omalizumab was for several years provided only in a dry powder formulation, which requires the reconstitution with a prepacked solvent with the help of a shaker at the treating clinician's office before injection. A prefilled syringe liquid formulation has become available in many countries.[56]

For the administration in patients with chronic spontaneous urticaria (or chronic idiopathic urticaria), the dosage is uniform, 300 mg per four weeks, subcutaneous, regardless of serum IgE levels and body weight.[57]

# 6 Manufacturing

Omalizumab is a glycosylated IgG monoclonal antibody produced by cells of an adapted Chinese hamster ovary (CHO) cell line.[2] The antibody molecules are secreted by the host cells in a cell culture process employing large-scale bioreactors. At the end of culturing, the IgG contained in the medium is purified by an affinity-column using Protein A as the adsorbent, followed by chromatography steps, and finally concentrated by UF/DF (paired ultra filtration/depth filtration). Currently, Omalizumab is manufactured at the Novartis' Huningue manufacturing site (France)[58] through a partnership agreement with Genentech.

# 7 Research

The website clinicaltrials.gov reveals that 144 clinical trials on omalizumab on various clinical indications have been finished or are in progress as of August 13, 2016. Among those more than 70 are multi-center, placebo-controlled phase II or III trials.[59] The tested indications are in the areas of allergic asthma, perennial and seasonal allergic rhinitis,[60][61] peanut allergy,[62] latex allergy,[63] atopic dermatitis,[64][65] chronic idiopathic urticaria (also called chronic spontaneous urticaria,[66][67] idiopathic anaphylaxis,[68] mastocytosis,[69] eosinophilic gastroenteritis, nasal polyposis,[70] and others. Some of those diseases are not caused by allergens and are generally not considered to be allergic diseases. Clinical trials in 2013 indicate that omalizumab is effective in patients with recalcitrant, antihistamine-resistant chronic idiopathic urticaria, including those cases of autoimmune cause.[38][39][71] Omalizumab has also been studied in combination with allergen-based specific immunotherapy (allergy shots) for the purpose of reducing anaphylactic reactions when receiving allergen immunizations and of accelerating immunization schedule and dosing, so as to achieve therapeutic effects in shorter treatment periods and in broader patient populations.[72][73][74]

In August 2013, a researcher at Leiden University Medical Center responsible for the TIGER trial was fired for unrelated research fraud. The TIGER trial was halted as a result.[75]

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- FDA

- AsthmaMatters Every Day
- Xolair

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