



Omalizumab in the treatment of allergy and asthma

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Omalizumab (Xolair[®], Novartis) is the first biologic agent introduced to specifically manage allergic disease. It is a recombinant DNA-derived humanized monoclonal immunoglobulin (Ig)G1 antibody with unique antihuman IgE binding specificities. Dosed every 2 to 4 weeks subcutaneously, it has the ability to neutralize free IgE in the blood and interstitial space in less than a day. It almost completely downregulates the high-affinity IgE receptors on basophils and mast cells over a period of several weeks. In multiple Phase II and III clinical studies, omalizumab has been shown to be safe and efficacious for treating allergic asthma and has been approved in Australia and the USA for this indication. It has proven effective in allergic rhinitis, latex sensitivity and peanut sensitivity and may be used in combination with standard allergy immunotherapy, providing a safer and more efficacious approach. Numerous clinical studies are in progress evaluating its use beyond allergic asthma.

In the USA alone, nearly 33 million people, including 9 million children, have a diagnosis of asthma, which in 1998 generated costs in excess of US\$12 billion [1]. Despite the emergence of highly effective medications, including both inhaled steroids and long-acting β -agonists, the outcomes, as measured by physician visits, emergency room utilization, and loss of school and work, have not changed significantly. In the most severe asthmatics there is a huge unmet need for a therapeutic approach, which would spare the use of oral or injected steroids to control the chronic process. The approval of an immunoglobulin (Ig)E blocker has provided hope for at least a subset of moderate and severe persistent asthmatics whose primary trigger is IgE mediated.

Overview of the market

What are the unmet needs of currently available therapies?

Asthma is marked by two major processes, airway inflammation and bronchospasm, both of which occur following the release of inflammatory compounds, some of which result from mast cell degranulation. Only antigen-specific immunotherapy has been shown to affect the basic immune causation of allergy and asthma. However, the efficacy rate, the complexity and potential danger of the procedure have limited its use to a small number of subspecialty physicians.

Pharmaceutical approaches, particularly with inhaled corticosteroids (ICSs), have provided an effective mechanism of dealing with the airway inflammation while sparing asthmatics from the

adverse effects of systemic corticosteroids. These medications have contributed to a decreased mortality rate in asthmatics, but have not been shown to stop the progression of the disease, particularly in the most severe asthmatics.

Inhaled β -agonists are commonly used for the treatment of bronchospasm. While remarkably effective in relieving acute symptoms, they also have no effect on disease progression, and chronic use may lead to tachyphylaxis and potential worsening of the underlying disease process [2].

The combination of ICSs and long-acting β -agonists, particularly when combined in the same device, have simplified asthma therapy, but have not produced the expected improvement in outcomes or compliance. Indeed the refill rates of combination drugs are not greater than those of the single agents alone, suggesting to many clinicians that the speed and efficacy of symptom relief has led patients into an instinctive pattern of intermittent use [3].

Other asthmatic pharmaceuticals include leukotriene modifiers, theophylline, and atropine-like drugs. These are useful in selective subsets of asthma, but due to a lack of overall efficacy and adverse events, may have limited long-term utilization.

Which competitor compounds/classes of compounds are in the clinic/late development?

Safer inhaled steroids and combinations of steroids and long-acting β -agents are in late Phase III approval status, but promise only an incremental improvement in asthma management.

Keywords:

anti-IgE, humanized antibody, asthma, rhinitis, latex, peanut, rush immunotherapy, Fc ϵ R1



Future Drugs Ltd

Type 4 cyclic AMP phosphodiesterase (PDE4) inhibitors are also in late Phase III developments with the possibility of an incremental impact on subsets of asthmatic patients.

Introduction to the compound

Omalizumab (Xolair[®], Novartis) is the first biologic agent approved for the treatment of allergic asthma that specifically interrupts disease progression by neutralizing the central mediator of Type 1 hypersensitivity, immunoglobulin (Ig)E. In normal mast cell biology, cross-linkage of bound IgE triggers release of inflammatory molecules. These molecules contribute to the airway inflammation and bronchospasm characteristic of asthma. Omalizumab is a humanized monoclonal IgG antibody with unique antihuman IgE binding specificities. This therapeutic anti-IgE binds to free human IgE in blood and in interstitial fluids with very high affinity. However, it does not bind to the IgE that is already bound by the high-affinity IgE receptors (FcεRI) on mast cells and basophils and to the low-affinity receptors (FcεRII, also referred to as CD23) on B-cells, granulocytes, platelets, and many other cell types. Unlike an ordinary anti-IgE antibody, this therapeutic anti-IgE does not activate mast cells and basophils. The anti-IgE also has the ability to bind to membrane-bound IgE-expressing B-cells, a major designed feature with the purpose of downregulating the development new IgE-producing cells [4]. The exact mechanism of action is more than simply tying up the antibodies to reduce the amount of IgE bound to mast cells [5].

Chemistry

Commercially available anti-IgE, omalizumab, is a recombinant DNA-derived humanized monoclonal IgG1 antibody developed by an aggregate of methods and techniques, referred to as 'antibody engineering' technology. For this humanized anti-IgE antibody, almost the entire framework segments in the variable domains and the entire constant domains of $\gamma 1$ heavy chain and κ light chain are derived from human Igs. The complementary determining regions (CDRs), which form the antigen-binding sites, are from a parental murine anti-IgE antibody. The CDRs, also referred to as hypervariable regions, are individually unique among antibodies and generally not recognized by the immune system. In vigorous studies, it was found that omalizumab does not induce antibody response in patients who had received multiple injections of the therapeutic antibody over a period of many months.

The first step in the development of this product was the establishment of a mouse hybridoma cell line which secretes an anti-IgE antibody with the desired set of binding specificities toward human IgE. The RNA from this hybridoma line was extracted and the genes encoding the variable regions of the antibodies were cloned and sequenced. Based on comparative analysis of existing antibody sequences, the CDR segments were identified. Genes encoding the whole-length humanized $\gamma 1$ and κ chains were then constructed. These recombinant heavy and light chain genes were inserted into an antibody expressing plasmid cassette, which was then transfected into a chinese hamster ovary (CHO) cell line host (a mammalian cell line used for the manufacturing of most of the antibody products approved for marketing by the US Food and Drug Administration [FDA]) for expressing the genes. The transfectants were screened for those that produced the humanized anti-IgE at high yield. The cell lines were then trained to grow in serum-free medium and under high shearing force, for adaptation to culturing in large bioreactor tanks and for suitability in downstream processing. The commercial omalizumab product is produced by CHO cell line in 12,000 liter bioreactors.

Pharmacodynamics

Omalizumab is now provided in a formulation for subcutaneous injection. After injection, the antibody dissipates in the circulation and interstitial space in less than 24 h with a bioavailability of about 60%. Early Phase I and II studies suggested a good clinical response when the average serum IgE was reduced to less than 25 $\mu\text{g/ml}$ with the minimum effective dose to achieve that goal being 0.016mg/kg (IU/ml) subcutaneously every 4 weeks adjusted for body weight and baseline IgE antigen load.

Pharmacokinetics & metabolism

It is estimated that omalizumab, in the absence of reaction with IgE, has a half-life of approximately 20 days, similar to that of native human IgG1. In most cases, the kinetics of the elimination of the injected anti-IgE is related to the relative concentrations of omalizumab and IgE, since the formation of the immune complex by the existing and the newly synthesized IgE consumes omalizumab. As concentrations of free IgE gradually fall to near zero, the concentrations of immune complexes formed by omalizumab and IgE gradually increase, reaching levels more than ten times the pretreatment

basal levels of IgE. This is because IgE is continually being synthesized by long living IgE-secreting plasma cells in the bone marrow which express very low levels of membrane-bound IgE and are not targets of anti-IgE. IgE has a half-life of 1 to 2 days, and the complexes of omalizumab and IgE have a half-life of about 20 days. The complexes are small, with the largest containing three omalizumab and three IgE molecules. In addition, these soluble and stable complexes do not deposit in the kidney and do not elicit antibody responses in treated patients.

Clinical efficacy

The efficacy of anti-IgE in severe 'allergic asthma' has been established in six major short- and long-term studies [6,7]. In the short term, 525 subjects with severe allergic asthma requiring daily ICSs were randomized to receive placebo or omalizumab subcutaneously every 2 or 4 weeks, with stable ICS doses for the initial 16 weeks of treatment and tapered during a further 12-week treatment period. Treatment resulted in significantly fewer asthma exacerbations per subject and lower percentages of subjects experiencing an exacerbation than placebo during the stable steroid and during the steroid reduction phases. ICS reduction was significantly greater with omalizumab treatment than with placebo and ICS discontinuation was more likely with anti-IgE treatment. Improvements in asthma symptoms and pulmonary function occurred along with a reduction in rescue β -agonist use. In the longer-term study, 460 patients continued a 24-week, double-blind extension phase of a previous 28-week core study. During the final 12 weeks, controlled attempts were made to gradually reduce ICS therapy. Both placebo and active patients were maintained on the lowest sustainable dose of beclomethazone dipropionate (BDP) and the use of other asthma medications was permitted during the extension phase. Omalizumab-treated patients experienced significantly fewer exacerbations compared with placebo during the extension despite a sustained significant reduction in their use of ICS [6,7]. Profiling the potential responder has been a constant clinical concern addressed by Bousquet and colleagues with a statistical review of the clinical database in adults [8].

Anti-IgE in allergic rhinitis has also been studied by Casale and colleagues [9]. A group of 536 patients aged 12 to 75 years with at least a 2-year

history of moderate to severe ragweed-induced seasonal allergic rhinitis and a baseline IgE level between 30 and 700 IU/mL were randomly assigned to receive omalizumab, 50 mg (n = 137), 150 mg (n = 134), or 300 mg (n = 129), or placebo (n = 136) subcutaneously just prior to ragweed season and repeated during the pollen season every 3 weeks in patients with baseline IgE levels of 151 to 700 IU/mL (four total treatments) and every 4 weeks in patients with baseline IgE levels of 30 to 150 IU/mL (three total treatments). Nasal symptom severity scores were significantly lower in patients who received 300 mg of omalizumab than in those who received placebo. A significant association was observed between IgE reduction and nasal symptoms and rescue antihistamine use.

Anti-IgE (TNX-901[®], Tanox Inc.) has been investigated in peanut anaphylaxis in 84 challenge-positive patients with a history of immediate hypersensitivity to peanuts [10]. Patients were randomly assigned TNX-901 (150, 300, or 450 mg) or placebo subcutaneously every 4 weeks for four doses, then underwent an oral food challenge within 2 to 4 weeks after the fourth dose. From a mean baseline threshold sensitivity of 178 to 436 mg of peanut flour, the mean increases in the oral food challenge threshold were 710 mg in the placebo group, 913 mg in the group given 150 mg of TNX-901, 1650 mg in the group given 300 mg of TNX-901, and 2627 mg in the group given 450 mg of TNX-901 ($p < 0.001$ for the comparison of the 450-mg dose with placebo). A 450 mg dose of TNX-901 increased the threshold of sensitivity to peanut in an oral food challenge from a level equal to approximately half a peanut (178 mg) to one equal to almost nine peanuts (2805 mg), potentially eliminating symptoms associated with accidental exposure.

Anti-IgE has also been studied in latex sensitivity during a 16-week randomized, double-blind, placebo-controlled period, followed by a 16-week open-label period during which all subjects received omalizumab [11]. Included were 18 healthcare workers with clinical symptoms of latex allergy (rhinitis, conjunctivitis and/or intermittent or persistent mild-moderate asthma). The conjunctival antigen challenge (CAC) test score was the primary outcome variable, and quantitative skin prick testing with latex allergens was a secondary outcome. At the end of the study, significantly more omalizumab-treated subjects (57.1%) had negative CAC scores compared with placebo (0/9,0%).

These patients had a significant improvement in conjunctival redness, chemosis, tears and itching. Placebo-treated patients did not improve until entering open-label omalizumab treatment. Skin reactions significantly decreased from baseline in subjects receiving omalizumab for 32 weeks. Skin reactions to 11, 33 and 100 IR dilutions of latex allergens decreased by 61, 49 and 64%, respectively.

Other conditions receiving consideration include atopic dermatitis, Churg Strauss, allergic bronchopulmonary aspergillosis, and polyposis.

Postmarketing surveillance

Anti-IgE was approved in June 2003 in the USA for the treatment of moderate-to-severe asthma not controlled with ICSs. Postmarketing studies (EXCELS) have been initiated but no data are available at this time.

Safety & tolerability

The safety database of omalizumab is built from the results of 19 completed Phase IIb/III/IIIb studies, ten completed Phase I/II studies, and seven ongoing Phase IIIb studies, with 4536 treated patients (including those treated in allergic rhinitis trials). There were three deaths in the trials in the active group and two in the control group with none related to the drug. Adverse events were reported in less than 3% of patients.

Since the basis of therapy is the complexing of IgG with IgE, extensive research was conducted into the search for an immune complex disease. Adverse events of fever, arthralgia, rash, urticaria, pruritis, dermatitis, and influenza-like symptoms were reported in 1–7% of all omalizumab-treated patients similar to the placebo group. In allergic asthma patients as a subgroup, the incident of arthralgia, rash, and pruritis were reported as over 1% higher in treated patients compared with controls.

Three treated patients were reported to have a systemic reaction described as anaphylactoid/anaphylaxis. Curiously, the reactions were delayed by as much as 90 mins, even when the drug was administered intravenously. Omalizumab was discontinued in two of the three reactions.

Malignancies were seen in 20 of 4127 (0.5%) omalizumab-treated patients compared with 5 of 2236 (0.2%) control patients. There was no pattern to the malignancies with breast, non-melanoma 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 were apparently enrolled with obvious cancer. The majority of patients were treated for 3 months or less and observed for less than 1 year. A panel of oncologists concluded after a blinded review that the association with cancer was unlikely to be drug related.

Pregnancy dangers have been well studied with this drug in cynomolgus monkeys. Subcutaneous doses up to 12-fold the maximum clinical dose did not produce maternal or embryo toxicity or teratogenicity and did not cause adverse effects on growth when administered throughout pregnancy and nursing periods.

While omalizumab has been designated as category B in pregnancy, IgG molecules of which it is constructed, are known to cross the placental barrier and there are no adequate and well-controlled studies of omalizumab in pregnant women or in human milk. Animal studies show the presence of omalizumab in breast milk.

Long-term adverse events are difficult to address since only a few patients have received this drug for more than 2 years. However, studies are underway (Evaluation of Xolair Clinical Effectiveness and Long term Safety: a 5-year study, Genetech, Novartis, currently in progress) which will prospectively address the effects over 5 years of administration.

Conclusion

Clinical trials strongly suggest that in adults and children with moderate-to-severe allergic asthma requiring daily ICS treatment, treated with anti-IgE decreases exacerbations, improves quality of life, reduces symptoms and respiratory functions, and allows decreased ICS dosages.

Expert opinion

Clinicians are having some difficulty in finding the exact niche of patients in which to apply this medication. In addition, the expense of new biologics, including this drug, severely limits widespread use. Current indications include several inexact criteria: moderate-to-severe persistent asthma uncontrolled with ICSs.

The issue of 'control' is at the heart of the problem since it is well known that only an extremely small portion of asthmatics cannot be controlled with maximum doses of ICSs, especially when combined with long-acting β -agonists. Indeed, many physicians report 'I have no uncontrolled

patients'. This would limit the use of the drug to patients who consistently exacerbate despite prescription and actual use of these drugs. One factor in exacerbation is compliance to a medical regimen. It is well documented that asthmatics refill their ICSs on average less than 4 months of therapy per year, most likely opting to take them on an 'as needed' basis [14]. It is unknown whether the higher doses of inhaled steroids are refilled at a higher rate than average. Therefore, if patients actually took their medications, it is conceivable that only a minute fraction would fit the approved indication for omalizumab.

However, 'control with inhaled steroids' ignores the potential for long-term problems with corticosteroids or the disease progression, which steroids likely do not affect. Therefore, most physicians, especially those with an eye toward the allergic component, feel there is market space for a drug that would affect the crucial pathways of IgE. Further complicating the use of this drug are issues that came about because of the nature of the clinical studies: the definition of allergy, its relationship to asthma, and the type of allergy that the drug treats.

The indication for asthma requires that the total level of IgE is between 30 IU/ml and 700 IU/ml [12]. This spread is based on the statistical risk of asthma but says nothing about the relationship of severity. Therefore, in a population of 1000 people, those having an IgE level of 400 IU/ml are more likely to have asthma than those with 30 IU/ml, but there is no proof that the ones with asthma at 400 IU/ml are more severe than those with an IgE level of 30 IU/ml. In fact, physicians have consistently experienced the observation that the level of IgE suggested in the dosing chart excludes (either too high or too low) many patients meeting the other criteria and have suggested that the dosing range should not define allergy [13].

The relationship of a positive skin test or RAST test and asthma is also an issue. The mere presence of a positive test and asthma does not equate to allergic asthma. Indeed the only clinical way (except for obvious cat-induced asthma) to make the association is a positive response to omalizumab. Under those conditions, especially when the response to drug is rapid and complete, the diagnosis of allergic asthma can be made. An alternative to establish a relationship between allergy and asthma might be to perform an inhalation challenge with suspected antigens, placing only those

positive responders on anti-IgE. This technique is both costly and potentially dangerous and is not in the practice pattern or skill set of the majority of specialists using this medication.

Furthermore since the drug was approved through studies carried out in multiple sites, only ubiquitous perennial allergens were considered. There is no evidence that anti-IgE performs any less with seasonal allergens than with perennial allergens. The pattern of non-compliance (likely because of lack of perceived need) suggests a periodic pattern of asthma, which might correspond to seasonal exposure, bearing in mind that viral infectious disease also has a seasonal pattern. Patients with significant seasonal allergens and asthma should be considered for therapy as often as those with perennial allergens.

The ultimate niche for this medication may involve those proven allergic patients with other comorbid conditions such as asthma that receive standard allergy immunotherapy. It is a consensus among specialists that success in terms of remission is achieved more dependably as a function of increased antigen doses. However, the possibility of anaphylaxis precludes overly aggressive antigen loads, and comorbid conditions such as asthma further place restrictions on the level of antigen load that can be achieved.

There is a recent trend observed whereby many allergists believe there is a role for concomitant use of standard allergy immunotherapy and anti-IgE. There are no theoretical contraindications for this dual therapy, and indeed some early advocates have demonstrated a synergy. Specialists feel that binding up IgE gives them a safety margin to be able to push very aggressive immunotherapy. Aggressive immunotherapy might shorten the usual extended course, and define an end point for both standard immunotherapy and omalizumab treatment. One of the most commonly cited reasons for failure of standard immunotherapy is the inability to use a dose necessary to achieve an effect in immunomodulation. Freed from the prospect of anaphylaxis, clinicians have a safer and more likely efficacious therapeutic strategy. anti-IgE may also be of significant value as a gateway to other disorders involving life-threatening diseases such as insect and food reactions.

Outlook

Following research advances, the field of allergy and immunology is about to receive the abundance of clinical tools. It is possible that newer

Highlights

- Allergy and asthma are very common and may overlap in some people.
- Crippling the allergic antibody may prevent both symptoms and the progression of the disease.
- Anti-IgE has few if any adverse reactions in the short-term.
- Anti-IgE may provide a safety margin for other forms of allergy treatment including standard allergy immunotherapy.

versions of anti-IgE that affect the process more ‘upstream’, reducing doses and costs, will initiate a near revolution in the management of allergic disease.

The FDA approval of omalizumab for adults and adolescent patients for asthma and the commercial success of omalizumab since its launch in July 2003 will lead to the many major activities in the next 5 years, including the expansion of

clinical trials of omalizumab in pediatric asthma, allergic rhinitis, peanut allergy, combination of anti-IgE and desensitization immunotherapy, and latex allergy.

Information resources

Anti-IgE is the first biologic developed and tested for one of the most common problems of mankind. The development and marketing has been rapid with efficacy proven and approval granted for asthma. There remain potential applications for this drug yet to be examined and many questions remain about the mechanism of action of anti-IgE. In addition, there appear to be refinements and expansion of the basic concept which may allow for greater efficacy.

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