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Omalizumab

Prop INN; USAN

Treatment of Allergic Rhinitis
Treatment of Asthma

E25
Hu-901
IGE-025
TNX-901
Xolair™

Immunoglobulin G, anti-(human immunoglobulin E Fc region) (human-mouse monoclonal E25 clone pSVIE26 γ-chain), disulfide with human-mouse monoclonal E25 clone pSVIE26 κ-chain, dimer

CAS: 242138-07-4

EN: 216352

Abstract

IgE levels play a crucial role in the mechanism of action responsible for asthma and allergic rhinitis. Omalizumab is a humanized anti-IgE antibody that binds to free IgE and prevents its binding to specific receptors on the surface of cells, thus preventing the release of immune mediators. Treatment of asthma and allergic rhinitis patients with omalizumab results in a decrease in serum IgE levels that is correlated with an improvement in the severity of symptoms and in the quality of life of the patients. Omalizumab has a good safety profile, with only mild to intermediate drug-related adverse events.

Introduction

Allergy has been defined as an abnormal reaction to an allergen, an ordinarily harmless substance that triggers an abnormal response in a sensitized individual. Allergic rhinitis is an inflammation of the mucus membranes of the nose that occurs in response to an airborne allergen. It is characterized by frequent or repetitive sneezing, runny or congested nose and itchiness of the nose, eyes and throat, although other symptoms may be also present (*e.g.*, headache, impaired smell, postnasal drip, conjunctival symptoms, sinusitis and other complicating respiratory symptoms). Depending upon the time of exposure, allergic rhinitis can be classified as perennial, seasonal or occupational: perennial allergic rhinitis (PAR) is the most prevalent form and is typically caused by exposure to dust mites, mold spores or animal dander, whereas seasonal allergic rhinitis (SAR) occurs in response to pollen or mold.

Asthma is a chronic inflammatory airway disease characterized by elevated bronchial tone, hypersecretion of airway mucus, hyperplasia of the airways smooth muscle and mucous glands, subepithelial fibrosis, submucosal edema and inflammation of the respiratory wall. Many cell types are involved in the pathogenesis of asthma, including mast cells, eosinophils and T lymphocytes. Asthma exacerbations (episodes of wheezing, breathlessness, chest tightness and cough, associated with airflow obstruction) may be triggered by exposure to allergens such as house dust mites or pollen, and also by conditions such as exercise, stress and respiratory infections.

The mechanism causing the appearance of asthma and allergic rhinitis is very similar. An allergen first binds to its specific IgE, which in turn binds to highly specific receptors on the surface of basophils and mast cells. This binding triggers the release of histamine, leukotrienes, eicosanoids and other proinflammatory mediators, which are ultimately responsible for the symptoms experienced by the patient. Therefore, a therapeutic strategy aimed at preventing the interaction of IgE with its specific cell surface receptors would be useful in the treatment and control of allergic diseases.

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Omalizumab (also known as Xolair® or rhuMAb E25) is a recombinant humanized construct of murine antibody MAE11 (1). About 95% of its sequence, including most of the antibody framework, is derived from human IgG_1. Omalizumab binds to circulating IgEs at the same site(s) on the Fc portion of the IgE molecule as the high-affinity receptor, FcERI, thereby blocking binding of IgE and inhibiting mediator release. The marked decrease in serum free IgE levels induced by omalizumab suggested a possible role for this agent in the treatment of allergic disorders (2).

Pharmacological Actions

Sedimentation analysis and size exclusion chromatography studies established that the molecular weight of omalizumab-human IgE complexes ranged from about 400,000 to about 1 million. The largest complex was a very stable hexamer consisting of 3 molecules of each immunoglobulin that seemed to have a cyclic structure. The size of complexes varied according to the ratio of omalizumab to IgE; *i.e.*, ratios close to 1:1 favored hexamer formation while an excess of IgE or omalizumab promoted formation of trimers (3). An aspartic acid residue located in the complementary-determining regions of the antibody seems to play an important role in isomerization and binding affinity (4).

Administration of [^{125}I]-labeled omalizumab to cynomolgus monkeys resulted in the formation of omalizumab-IgE complexes similar to those detected *in vitro* with human IgE. Again, the distribution of complexes within this molecular weight range depended on the baseline concentration of IgE present in each animal; *i.e.*, an excess of omalizumab or IgE promoted trimer formation, whereas similar molar ratios resulted in the formation of hexamers. No interaction of omalizumab with other serum proteins was detected (5).

Pharmacokinetics and Metabolism

Studies conducted in cynomolgus monkeys showed that omalizumab was not specifically taken up into any organ or tissue compared to blood. More than 90% of circulating omalizumab was present in its intact form and no metabolites were detected in serum. Urinary excretion was the primary route of elimination, and most of it was not excreted intact. Omalizumab did not accumulate in the kidney, which was consistent with the lack of evidence of immune complex disease found in toxicology studies. Administration of omalizumab decreased IgE clearance through formation of omalizumab-IgE complexes and thus increased total serum IgE levels, although these changes had no toxicological consequences (5).

The pharmacokinetic and pharmacodynamic profile of omalizumab administered i.v. or s.c. has been determined in approximately 1950 adults and children, and similar results have been obtained regardless of age, sex, race or indication (6, 7). Similar binding affinity to omalizumab has been reported for human IgE and cynomolgus monkey IgE (K_d = 0.06 and 0.19 nM, respectively) (8). In humans, omalizumab has an average terminal half-life of 22 ± 8.7 days, a distribution volume of 95.6 ± 35 ml/kg and a systemic clearance of 3.5 ± 1.7 ml/kg/day (9). A randomized, double-blind, placebo-controlled study in 9 mild asthmatics found that omalizumab reached high levels in the bronchoalveolar lavage fluid from central and distal airways after i.v. administration. In this case, mean total IgE levels in the bronchoalveolar lavage fluid did not change significantly after 27 days of treatment with omalizumab, thus suggesting that the rate of complex clearance was similar to the rate of complex formation (10).

Clinical Studies

Studies conducted in humans have shown that omalizumab decreases free serum IgE levels in a dose- and baseline IgE-dependent manner (6). Free serum levels equal to 60% and 20% of baseline have been reported in humans 21 days after administration of weekly omalizumab doses of 0.15 mg/kg s.c. or 0.50 mg/kg i.v., respectively (7). Higher decreases have also been reported by other authors (11, 12). A study in 35 allergic asthma patients treated with 0.016 mg/kg/IgE [IU/ml] of omalizumab every 4 weeks found that the compound decreased circulating levels of mediators (*e.g.*, IL-13) and histamine release from basophils (13). Long-term administration of omalizumab to humans has been associated with a lower reactivity to allergens, as shown by changes in serum IgE levels and in the number of IgE plaque-forming cells (63% decrease and 78% decrease, respectively, after 168 days of treatment) (14).

Allergic rhinitis

The use of omalizumab in the treatment of seasonal allergic rhinitis (SAR) has been analyzed by different clinical trials conducted with ragweed or birch pollen. In a randomized clinical trial, 251 adult patients suffering from SAR and with a positive skin test response to birch pollen received either 300 mg s.c. of omalizumab or placebo 2-3 times during the season. Treatment with omalizumab significantly improved the daily nasal symptom scores, the average number of rescue medication tablets taken per day, the percentage of days with usage of any SAR medication and the quality of life of the patients. Serum-free IgE levels were much lower with omalizumab and were associated with clinical efficacy (15). The original work on ragweed-induced SAR reported that treatment with omalizumab decreased serum-free IgE levels in a dose- and baseline IgE-dependent manner, although the number of subjects with undetectable free IgE levels in serum was too low to confirm efficacy of the treatment (16). However, a later randomized, double-blind, placebo-controlled trial in 536 patients with ragweed-induced SAR

Table I: Clinical studies of omalizumab in patients with allergic rhinitis and/or conjunctivitis (from Prous Science Integrity®).

Indication	Treatments	n	Conclusions	Ref.
Randomized, double-blind, multicenter	Omalizumab, 50 mg sc every 3 wk x 4 doses (n=137) Omalizumab, 150 mg sc every 3 wk x 4 doses (n=134) Omalizumab, 300 mg sc every 3 wk x 4 doses (n=129) Placebo x 4 doses (n=136)	536	Omalizumab was safe and effective in decreasing serum-free IgE levels and improved symptoms of seasonal allergic rhinitis in a dose-dependent fashion	17
Randomized, double-blind, multicenter	Omalizumab, 50 mg sc 1x/3-4 wk x 12 wk (n=112) Omalizumab, 150 mg sc 1x/3-4 wk x 12 wk (n=100) Omalizumab, 300 mg sc 1x/3-4 wk x 12 wk (n=112) Placebo (n=111)	435	Omalizumab significantly improved rhinitis-related quality of life during the allergy season in patients with seasonal allergic rhinitis	18
Randomized, double-blind, multicenter	Omalizumab, 150-300 mg (or 225-375 mg sc 1x/2 wk depending on baseline serum total IgE and body weight) sc 1x/4 wk x 16 wk (n=144) Placebo (n=145)	289	Omalizumab was well tolerated and effective in moderate to severe perennial allergic rhinitis	19, 20
Randomized, multicenter	Omalizumab, sc (dose adjusted to baseline IgE and body weight) + Specific immunotherapy for birch pollen (prior to and during the pollen season) (n=22) Omalizumab, sc (dose according to baseline IgE and body weight) + Specific immunotherapy for grass pollen (prior to and during the pollen season) (n=23) Placebo + Specific immunotherapy for birch pollen (prior to and during the pollen season) (n=22) Placebo + Specific immunotherapy for grass pollen (prior to and during the pollen season) (n=24)	91	Omalizumab was effective in reducing sulfido-leukotriene release to birch and grass pollen in children and adolescents	21
Randomized, double-blind, multicenter	Omalizumab, 150-300 mg 1x/4 wk or 225-375 mg 1x/2wk (dose adjusted to baseline IgE and body weight) sc x 24 wk + Specific immunotherapy (ALK-Abello) for birch/grass pollen (4 mo prior to pollen season) Placebo + Specific immunotherapy (ALK-Abello) for birch/grass pollen (4 mo prior to pollen season)	225	The combination of specific immunotherapy and omalizumab was more effective in reducing allergic mediators in nasal secretion, symptoms and rescue medication needed when compared with specific immunotherapy alone in birch and grass pollen-induced seasonal allergic rhinoconjunctivitis	22, 23

found that s.c. administration of 300 mg omalizumab every 3-4 weeks resulted in a significant decrease in serum-free IgE levels that correlated with improved nasal symptom scores and lower use of rescue histamines. Omalizumab also significantly improved the quality of life of the patients (17, 18). The results of these allergic rhinitis studies and the ones that follow are summarized in Table I.

Perennial allergic rhinitis (PAR) has also been evaluated as a possible indication for omalizumab. A randomized, double-blind, placebo-controlled trial included 289 patients with moderate to severe PAR. After s.c. administration of either omalizumab 150-300 mg every 4 weeks, omalizumab 225-375 mg every 2 weeks or placebo for 16 weeks, the severity of nasal and ocular symptoms was found to be significantly lower in omalizumab-treated patients than in placebo-treated patients (1.07 *vs.* 1.38 for mean nasal symptoms and 0.71 *vs.* 0.92 for mean ocular symptoms). PAR control was detected in 27.8% of omalizumab-treated patients and 9.7% of placebo-treated patients and the daily number of rescue medication tablets was lower after treatment with omalizumab (0.06 *vs.* 0.13 with placebo). These effects also improved the patients' quality of life (19, 20).

In an effort to further improve the patients' response to treatment, researchers assessed the efficacy of combining omalizumab with specific immunotherapy against allergens causing SAR. A phase III placebo-controlled study conducted in children or adolescents suffering from SAR induced by birch and grass pollen found that the amount of sulfido-leukotrienes (inflammatory mediators released as a result of binding of allergen to IgE on mast cells and basophils) decreased in the groups of patients receiving omalizumab combined with specific immunotherapy (21). The combination treatment decreased the median use of rescue medication by 71% and allergy symptoms by 40% compared to specific immunotherapy alone (22). Therefore, anti-IgE therapy seemed to confer a protective effect against IgE-mediated symptoms against different allergens and over different organ systems, which led to a higher efficacy against allergic rhinitis compared to specific immunotherapy alone. The combination therapy would be especially effective for polysensitized patients (23).

Asthma

One of the first studies of omalizumab in asthma patients was a multicenter, double-blind, parallel, 11-week study that assessed the effects of omalizumab on the amount of allergen needed to cause a 15% early

asthmatic response (PC15) in 19 allergic asthmatics. Intravenous administration of omalizumab decreased mean serum-free IgE levels by 87-91% that correlated with an increase in the allergen PC15 value (11).

In a multicenter, placebo-controlled, double-blind study, 317 asthma subjects treated with inhaled or oral corticosteroids were randomized to receive either placebo or one of two regimens of omalizumab: a low-dose regimen (2.5 μg/kg/ng IgE/ml) or a high-dose regimen (5.8 μg/kg/ng IgE/ml). The subjects received the study medication intravenously on days 0, 4 and 7, and then every 2 weeks for 20 weeks; treatment with corticosteroids was maintained for the first 12 study weeks and was then lowered in an effort to discontinue the therapy. Improvement in asthma symptom scores was similar in both omalizumab groups after 12 and 20 weeks of treatment, and the percentage of subjects who were able to decrease the corticosteroid dose by more than 50% was slightly higher in the high-dose group than in the low-dose group for both inhaled corticosteroids (51% *vs.* 49%) and oral corticosteroids (78% *vs.* 57%). In contrast, more patients in the low-dose group discontinued treatment with oral (43% *vs.* 33%) and inhaled (23% *vs.* 18%) corticosteroids. Both omalizumab regimens improved the mean forced expiratory volume in one second (FEV_1), peak expiratory flow rates, number of asthma exacerbations and quality of life of the subjects (12). It has been suggested that treatment with omalizumab could decrease the dose of corticosteroids needed by the patient through a decrease in airway inflammation (24).

A randomized, multinational, phase III, double-blind, placebo-controlled study included 546 patients aged 12-76 years with moderate to severe allergic asthma, who were randomized to receive s.c. omalizumab (a minimum monthly dose of 0.016 mg/kg/IgE [IU/ml], adjusted according to serum-free IgE levels and body weight at baseline) or placebo for 28 weeks. The patients also received a stable treatment with steroids (beclomethasone dipropionate, BDP) during the first 16 study weeks, after which the BDP dose was lowered until the minimum effective dose was reached; the latter was maintained until the end of the study period. Treatment with omalizumab significantly decreased the number of asthma exacerbations, the need for BDP administration in order to keep symptoms under control (25), the time to first exacerbation (26) and the number of hospitalizations due to serious asthma exacerbations (27). Higher FEV_1 values were measured in omalizumab-treated patients throughout the study period, indicating an improved respiratory function (28). The percentage of asthma control days was significantly higher in the group of patients treated with omalizumab (29). Another phase III, double-blind, placebo-controlled trial that used the same study design in 525 patients with severe allergic asthma confirmed these results and also reported that omalizumab-treated patients were significantly less likely to have their first asthma exacerbation before placebo-treated patients (30, 31). The use of fluticasone instead of BDP did not affect the efficacy and safety of treatment with omalizumab (32). Furthermore, the efficacy of omalizumab was independent of the severity of asthma (33) and the agent improved the quality of life of patients suffering from allergic asthma (34).

Very recently, a subgroup analysis was conducted in patients with severe allergic asthma who were receiving fluticasone (1000-2000 μg/day). The patients were randomly allocated to receive s.c. injections of omalizumab (at least 0.016 mg/kg/IgE [IU/ml) or placebo once every 2 or 4 weeks for a total of 32 weeks. Response to omalizumab was measured as reduction in fluticasone use and in the rate of asthma exacerbation episodes, and it was found to be higher in patients with more severe asthma (as established by FEV1 values or by having a prior history of emergency treatment in the year before conducting the study) (35).

Omalizumab is also effective in the treatment of childhood asthma. In a double-blind, randomized, placebo-controlled study, 334 males and premenarchal females aged 6-12 years old who suffered from moderate to severe asthma and needed treatment with inhaled corticosteroids were randomized to receive either placebo or a omalizumab dose adjusted to body weight and initial serum IgE levels. Compared to placebo, omalizumab increased the percentage of patients who decreased their BDP dose, induced a greater reduction in the BDP dose (100% *vs.* 66.7%) than placebo, and made it possible for more patients to discontinue treatment with BDP (55% vs. 39%). Omalizumab also decreased the need for rescue medication and the incidence and frequency of severe exacerbations. Median serum-free IgE levels decreased by 95-99%, changing from 133-790 IU/ml at baseline to 6-9 IU/ml after treatment with omalizumab; in contrast, treatment with placebo did not modify serum-free IgE levels (36).

Finally, the possible use of omalizumab administered as an aerosol was assessed in a randomized, double-blind study in 33 subjects with mild allergic asthma. Compared to placebo, once-daily administration of aerosolized omalizumab did not induce any significant changes in serum IgE levels or attenuation of early response to allergen after treatment for 2-8 weeks, despite the detection of omalizumab in serum. Therefore, the aerosol route of administration does not seem adequate for monoclonal antibodies in the treatment of asthma (37).

Safety

Early studies reported mild or moderate adverse events related to asthma symptoms or upper respiratory infections in both omalizumab-treated and placebo-treated patients (6, 7). These initial results were later confirmed by later, large-scale studies. The most common adverse events reported for omalizumab are upper respiratory tract infections, headache, sinusitis and viral infections, with similar incidences in omalizumab-treated and placebo-treated patients (38). No drug-related serious

Table II: Clinical studies of omalizumab in patients with asthma (from Prous Science Integrity®).

Indication	Treatments	n	Conclusions	Ref.
Randomized double-blind, multicenter	Omalizumab, 0.016 mg/kg/IgE IU/ml sc 1x/1mo + Beclomethasone dipropinate, 770.5 (mean) µg/d (tapered after 16 wk over 8 wk and stable dose 4 more wk) x 28 wk (n=274) Placebo + Beclomethasone dipropionate, 770.5 /mean] mg/d (tapered after 16 wk over 8 wk and stable dose 4 more wk) x 28 wk (n=272)	546	Omalizumab was safe and effective in decreasing the risk of asthma exacerbation, increasing FEV_1, morning and evening PEF and proportion of time in which moderate to severe allergic asthma was controlled and reducing β-agonist rescue medication requirements in patients with moderate to severe asthma	26
Randomized, double-blind, multicenter	Omalizumab, > 0.016 mg/kg sc 1-2x/mo x 28 wk (n=767) Placebo (n=638)	767	Omalizumab reduced hospitalization due to serious asthma exacerbation in both adults and children	27
Randomized, double-blind	Omalizumab, ≥ 0.016 mg/kg/IgE IU/ml sc 1x/1 mo + Beclomethasone dipropionate (tapered after 16 wk over 12 wk) x 28 wk + follow-up for 5 more mo Placebo + Beclomethasone dipropionate (tapered after 16 wk over 12 wk) x 28 mo + follow-up for 5 more mo	525	Omalizumab was safe and effective in reducing inhaled corticosteroid usage and preventing asthma exacerbations in moderate to severe allergic asthma	30, 31
Randomized, double-blind, multicenter	Omalizumab, 150-300 mg sc 1x/1 mo or 225-375 mg sc 1x/2 wk (adjusted to weight and serum total IgE) + Fluticasone propionate, 1369 (mean) mcg/d inhalation (tapered after 16 wk over 12 wk) x 32 wk (n=126) Placebo + Fluticasone propionate, 1369 (mean) µg/d inhalation (tapered after 16 wk over 12 wk) (n=120)	246	Omalizumab was safe and well tolerated and effective in permitting a dose reduction in fluticasone propionate and improving quality of life and FEV_1 in severe allergic asthma	32, 34
Randomized, double-blind	Omalizumab, 1 mg inhalation od x 56 d (n=12) Omalizumab, 10 mg inhalation od x 56 d (n=10) Placebo (n=11)	33	Omalizumab was safe but did not reduce the airways response to inhaled allergen in allergic asthma. The aerosol administration might be more immunogenic than the parenteral route	37
Randomized, double-blind, multicenter	Omalizumab, >0.016 mg/kg/IgE IU/ml sc 1x/4 wk x 12 mo (n=245) Placebo (n=215)	460	Long-term treatment with omalizumab was safe and well tolerated in moderate to severe asthma	38
Randomized, double-blind, multicenter, pooled data	Studies I/II: (Studies 008 and 009) Omalizumab, >0.016 mg/kg/IgE IU/ml sc 4/wk q2-4 wk + inhaled corticosteroids (tapered after 16 wk over 12 wk) x 76 wk Placebo + inhaled corticosteroids (tapered after 16 wk over 12 wk) x 76 wk Study III: (Study 011) Omalizumab, >0.016 mg/kg/IgE IU/ml sc 4/wk q2-4 wk + fluticasone (tapered after 16 wk over 16 wk) x 76 wk Placebo + inhaled corticosteroids (tapered after 16 wk over 16 wk) x 76 wk	1412	Omalizumab was well tolerated and effective in improving asthma exacerbation episodes and quality of life in patients at high risk of serious asthma-related morbidity and mortality	40
Randomized, double-blind, multicenter, pooled data	Studies I/II: Omalizumab, >0.016 mg/kg/IgE IU/ml sc 1x/2-4 wk + Beclomethasone dipropionate, 420-1008 µg/d x 52 wk (tapered after 16 wk over 8 wk) x 52 wk (n=542) Placebo + Beclomethasone dipropionate, 420-1008 µg/d (tapered after 16 wk over 8 wk) x 52 wk (n=529) Study III: Omalizumab, >0.016 mg/kg/IgE IU/ml sc 1x/2-4 wk x 52 wk + Beclomethasone dipropionate, 420-1008 µg/d (tapered after 16 wk over 8 wk) x 28 wk (n=225) Placebo + Beclomethasone dipropionate, 420-1008 µg/d (tapered after 16 wk over 8 wk) x 28 wk (n=109)	1405	Omalizumab reduced the risk of serious asthma exacerbations requiring hospitalization in moderate to severe allergic asthma	41

(Continued)

Table II (Cont.): Clinical studies of omalizumab in patients with asthma (from Prous Science Integrity®).

Indication	Treatments	n	Conclusions	Ref.
Randomized, double-blind	Omalizumab, >0.016 mg/kg/IgE IU/ml sc 1x/4 wk + Beclomethasone dipropionate (tapered after 16 wk over 12 wk) x 28 wk (n=225) Placebo + Beclomethasone dipropionate (tapered after 16 wk over 12 wk) x 28 wk (n=109)	334	Omalizumab was safe, well tolerated and effective in reducing the requirement for inhaled corticosteroids and number of disease exacerbations in children with asthma	42
Randomized, double-blind, multicenter	Omalizumab, 0.006 mg/kg/IgE IU/ml iv q2 wk x 6 wk (n=106) Omalizumab, 0.014 mg/kg/IgE IU/ml iv q2 wk x 6 wk (n=106) Placebo (n=105)	317	The low dose of omalizumab decreased exacerbations and the use of corticosteroids and rescue medications, while being well tolerated	43
Randomized, double-blind, multicenter	Omalizumab, 0.016 mg/kg/IgE IU/ml 1x/4 wk + Beclomethasone dipropionate, 500-1000 μg/d x 16 wk Placebo + Beclomethasone dipropionate, 500-1000 μg/d	35	Omalizumab was effective in allergic asthma	44
Randomized, double-blind,	Omalizumab x 9 wk Placebo	19	While being safe, omalizumab reduced circulating IgE and inhibited early and late phase responses to inhaled allergen in allergic asthma	45
Double-blind, multicenter	Omalizumab, 2 mg/kg iv sd → 1.0 mg/kg iv @ 7, 14 d and q2 wk up to 10 wk (n=10) Placebo (n=9)	19	Omalizumab may be effective in allergic asthma	46
Randomized, single-blind	Omalizumab, 0.15 mg/kg sc x 3 wk Omalizumab, 0.50 mg/kg iv x 3 wk Placebo	12	Omalizumab was safe and reduced serum-free IgE levels in moderate to severe asthma	47
Randomized, double-blind	Omalizumab, 2 mg/kg iv sd → 1.0 mg/kg iv 1x/2wk x 12 wk Placebo	9	Systemic omalizumab was effective in reducing early asthmatic response in asthma	48
Randomized, double-blind, multicenter, pooled data	Study I: Omalizumab, 2 mg/kg iv sd (d 0) → 1 mg/kg iv 1x/7-14 d x 10 wk Placebo Study II: Omalizumab Placebo Study III: Omalizumab, 1.25 μg/kg/ng IgE/ml iv 2x/4 d → 2.5 μg/kg/ng IgE/ml iv 1x/2 wk x 20 wk + β-Agonists + Corticosteroids (dose tapered during the last 8 wk) Omalizumab, 2.9 μg/kg/ng IgE/ml iv 2x/4 d → 5.8 μg/kg/ng IgE/ml iv 1x/2 wk x 20 wk + β-Agonists + Corticosteroids (dose tapered during the last 8 wk) Study IV: Omalizumab, 150-300 mg iv 1x/4 wk x 4 mo + Beclomethasone dipropionate (dose reduced 25% q2 wk) Omalizumab, 225-375 mg iv 1x/2 wk x 4 mo + Beclomethasone dipropionate (dose reduced 25% q2 wk) Placebo		Omalizumab was safe and effective in asthma	49
Randomized, double-blind, multicenter	Omalizumab, 150-300 mg (or 225-375 mg q2 wk depending on weight and serum IgE) sc q4 wk x 54 wk Placebo		Long-term treatment with omalizumab showed a sustained reduction in exacerbations and steroid medication in patients with previously inadequately controlled allergic asthma	51

adverse events have been reported for adult or pediatric patients, and no evidence of immune complex disease or development of antibodies against omalizumab has been found, thus confirming that treatment with omalizumab is both safe and well tolerated, even in patients at high risk of serious asthma-related morbidity and mortality (12, 15-17, 19, 20, 25, 30, 32, 33, 36, 39).

Results of some of these clinical studies of omalizumab in asthma, as well as others not described above (40-51), are summarized in Table II.

Australia's Therapeutic Goods Administration (TGA) has approved omalizumab for the treatment of moderate allergic asthma in adults and adolescents, representing the first approval for the product. The approval followed the earlier proposal by the country's Drug Evaluation Committee that the drug be made available for those patients who are already being treated with inhaled steroids and who have elevated levels of serum IgE. Omalizumab (Xolair®) is administered as an s.c. injection every 2-4 weeks. A BLA for the drug was filed in the U.S. in 2000, as well as submissions for approval in the E.U., Switzerland, Australia and New Zealand. Genentech and Novartis received a complete response letter from the FDA in July 2001, in reply to which the companies are planning to submit a BLA ammendment in the fourth quarter of 2002 (52).

Source

Discovered by Genentech, Inc. (US); licensed to Novartis AG (CH) and Tanox, Inc. (US).

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