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Omalizumab (Xolair™): A Brief Review

Indications

Omalizumab is indicated for adults and adolescents (12 years of age and older) with moderate-to-severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Omalizumab has been shown to decrease the incidence of asthma exacerbations in these patients.[1]

Clinical Pharmacology

Omalizumab (rhuMAb-E25) is a nonanaphylactogenic recombinant humanized monoclonal antibody to immunoglobulin E (anti-IgE) produced by a Chinese hamster ovary cell suspension culture. It is directed to the FcεR1-binding domain of human IgE.[2,3] Ordinarily anti-IgE antibodies cross-link IgE bound to basophils or mast cells triggering degranulation and anaphylactoid reactions. Omalizumab inhibits the binding of IgE to mast cells without provoking mast cell activation.[2]

Several manufacturers have developed antibodies directed against the portion of the IgE molecule that binds to the high-affinity Fcε receptor. Such an antibody should be able to bind free IgE molecules and then either remove the IgE from the circulation as immune complexes or else prevent the IgE from binding the Fcε receptor due to steric hindrance.[2,3] By either mechanism, the binding of IgE to cell-membrane receptors is blocked, thereby inhibiting the release of inflammatory mediators.[4]

Genentech, Novartis, and Tanox developed omalizumab. Several other anti-IgE antibodies, such as anti-IgE antibody 17-9, BSW17, and CGP 51901, all of which also recognize the FcεRi binding site of IgE have also been evaluated clinically. These products were created by developing mouse antibodies that bound free IgE, but did not stain mast cells. These were then humanized by retaining the antigen combining site and engineering this into a human immunoglobulin (IgG1 for omalizumab and IgG2b for anti-IgE antibody 17-9) molecule.[2,5,6,7] Omalizumab is more than 95% human.[4]

The maximal size of the omalizumab-IgE immune complexes has been two to three IgE molecules bound to two to three molecules of omalizumab. This small size does not fix complement.[3]

IgE has a well-defined role in atopic conditions and the allergic response. The role of IgE in asthma is less clear. A trait for serum total IgE increase is coinherited with a trait for bronchial hyperresponsiveness, although serum total IgE levels were not found to correlate with bronchial hyperresponsiveness, suggesting that other regulatory factors are involved.[8] Allergen-induced inflammatory responses are observed in some types of clinical asthma, where allergen exposure can increase airway responsiveness in sensitized individuals. In allergic subjects, this can lead to worsening and persistence of asthma symptoms.[9]

Many patients with asthma have evidence of IgE-mediated hypersensitivity to airborne allergens, particularly among children with asthma. More than 85% of children with asthma have shown positive skin tests to one or more airborne allergens.[2] In some studies, however, asthma episodes have not appeared more frequently during allergy seasons, and allergen avoidance led to only modest reductions in nonspecific bronchial responsiveness. Only extreme forms of avoidance produced significant clinical benefit.[2]

IV administration of omalizumab attenuates the early and late phase responses to inhaled allergen in subjects with asthma. IV administration of omalizumab in a double-blind, placebo-controlled study enrolling 19 allergic asthmatic subjects reduced serum IgE, increased the dose of allergen needed to provide an early asthmatic response, reduced the mean maximal fall in FEV_1 during the early response, and reduced the mean maximal fall in FEV_1 during the late response. Enrolled patients had mild asthma requiring only inhaled beta agonist therapy, and positive skin prick tests to house dust mite, cat pelt, or rye grass. They received therapy with either placebo or omalizumab 0.5 mg/kg on nine visits (days 1, 7, 14, 21, 28, 35, 42, 49, and 56).

The mean maximal FEV_1 during the early response declined from 30% at baseline to 18.8% in the omalizumab group; in the placebo group the mean maximal FEV_1 was 33% at baseline and 34% after placebo ($P = 0.01$). The mean maximal FEV_1 during the late phase declined from 24% at baseline to 9% after omalizumab, and from 20% at baseline to 18% after placebo ($P = 0.047$).

The concentration of allergen required to cause bronchoconstriction rose in the omalizumab group. Skin test reactivity was not altered by omalizumab therapy. Methacholine PC_{20} was not significantly improved overall, although two subjects had substantial increases in doubling doses. Free IgE concentration decreased rapidly in the omalizumab group and remained suppressed throughout the course of the study; total IgE levels were increased in the omalizumab group as a result of reduced clearance of bound IgE.[10]

In another study to determine if omalizumab reduces the early asthmatic response to inhaled allergens (expressed as the provocative concentration of allergen inducing a 15% fall in forced expiratory volume in 1 second in adult subjects with mild asthma), 20 subjects with mild asthma who required only as-needed beta agonists for asthma control and had a highly positive allergy skin prick test to at least one common aeroallergen were enrolled.

After the prestudy allergen challenge, the patients received either placebo or omalizumab 2 mg/kg on day 1 followed by 1 mg/kg on days 7, 14, 28, 42, 56, and 70. The PC_{15} to allergen increased after omalizumab treatment, with increases of 2.3, 2.2, and 2.7 doubling doses during omalizumab treatment, and –0.3, +0.1, and –0.8 doubling doses during placebo ($P < 0.002$).

Methacholine PC_{20} also improved slightly in the omalizumab group (0.9 doubling doses), but not in the placebo group. Serum free IgE levels decreased from 287.8 ng/mL to 30 ng/mL at day 77 of the study ($P < 0.001$). Serum free IgE levels were below the level of detection in 7 of 10 omalizumab-treated patients. A greater than two doubling dilution increase in allergen PC_{15} was seen in one of three subjects with incomplete serum free IgE suppression and in six of seven with complete serum free IgE suppression.

Serum concentrations of total omalizumab rose to 30,930 ng/mL at 77 days. Total serum IgE concentration increased to 2,402.2 ng/mL from its baseline level of 613.5 ng/mL. Respiratory symptoms, bronchodilator need, peak flow, and FEV_1 were unchanged in both groups. Allergen skin test sensitivity were also unchanged.[9]

In an assessment of 35 patients with moderate-to-severe asthma treated with omalizumab in a clinical trial, free IgE levels were reduced to less than 10 international units/mL in all patients. IL-13 was reduced ($P < 0.01$). Histamine release from basophils was reduced ($P < 0.01$), but returned to baseline 3 months after discontinuation of therapy. Airway resistance was reduced ($P < 0.05$) and the provocative concentration inducing a 20% reduction in FEV_1 was also reduced ($P < 0.05$). Peripheral eosinophil count was reduced ($P < 0.01$) and the area of the wheal reaction in the skin prick test was reduced ($P < 0.01$).[11]

In patients with seasonal allergic rhinitis, omalizumab was associated with an anti-inflammatory effect on cellular markers in the blood and nasal tissue. Compared with placebo-treated patients, reductions were observed in blood eosinophils, free IgE, eosinophil peroxidase-positive staining cells in nasal biopsy specimens, and the number of IgE-positive staining cells.[12]

Omalizumab can reduce airway inflammation assessed by exhaled nitric oxide levels in pediatric patients with asthma. Omalizumab prevented an increase in airway inflammation during inhaled corticosteroid withdrawal; exhaled nitric oxide levels rose 35% in placebo-treated patients during inhaled corticosteroid withdrawal, while declining 25% in omalizumab-treated patients.[13]

In animal studies omalizumab also reduced skin reactions to ragweed.[3] Such effects have generally not been observed in human studies for which skin test results were reported.[9,10,14]

Aerosolized delivery of omalizumab 1 and 10 mg doses did not inhibit the airway response to inhaled allergen in allergic asthmatic subjects.[15]

Pharmacokinetics

Omalizumab bioavailability is 62% when dministered subcutaneously. Omalizumab is slowly absorbed reaching a peak concentration after an average of 7 to 8 days. Following multiple doses, the area under the serum concentration-time curve (AUC) from day 1 to day 14 at steady-state was up to 6-fold that of the first dose.[1] Steady-state concentrations were achieved by days 14 to 28 following doses on days 0, 7, 14, and 28.

Omalizumab has a terminal half-life of 2.9 weeks after multiple-dose IV and SC doses.14 In asthma patients omalizumab serum elimination half-life averaged 26 days. Doubling of body weight approximately doubled apparent clearance.[1] Dosage adjustments do not appear necessary for age (12 to 76 years of age), race, ethnicity, or gender.[1]

The clearance of omalizumab involves IgG clearance processes as well as clearance via specific binding and complex formation with IgE. IgG is hepatically degraded in the liver reticuloendothelial system and endothelial cells. Intact IgG is also excreted in bile. Omalizumab: IgE complexes are eliminated by interactions with Fcε receptors within the reticuloendothelial system at rates greater than IgG clearance.[1]

The half-life of the omalizumab-IgE complex is 21 days, in contrast to free IgE which has a halflife of 1 day.[3] With doses sufficient to complex all free IgE in animal studies, total IgE concentrations increased 6-fold compared with baseline, while free IgE levels decreased to undetectable.[3] Similar results have been observed in humans, with reductions in free IgE observed within 5 minutes of IV and 24 hours of SC injection. Levels declined below the level of detection for 4 to 6 weeks, while total IgE levels increased 4- to 6-fold.[3] Serum total IgE levels remain increased for up to 1 year after discontinuation of omalizumab therapy.[1]

Comparative Efficacy

Asthma (FDA-Approved Indication)

Omalizumab was evaluated in a phase III, double-blind, placebocontrolled study enrolling 525 patients 12 to 75 years of age with severe allergic asthma who were symptomatic despite daily inhaled corticosteroids. Patients were required to have positive immediate responses to skin-prick testing to at least one common allergen, total serum IgE of 30 international units/mL to 700 international units/mL, FEV_1 reversibility of at least 12% within 30 minutes of albuterol administration, baseline FEV_1 between 40% and 80% of predicted, and treatment with 420 to 840 mcg/day of beclomethasone dipropionate or its equivalent for at least 3 months prior to randomization. More than 99% of the patients met National Heart, Lung, and Blood Institute criteria for severe persistent asthma.

Patients were switched to beclomethasone dipropionate if they were receiving an alternate corticosteroid and maintained on a steady dose for at least 4 weeks prior to randomization. Patients were randomized to receive omalizumab (268 patients) SC every 2 or 4 weeks, depending on pretreatment serum IgE and body weight, or placebo (257 patients). Inhaled corticosteroid doses were kept stable for the first 16 weeks of the study, then tapered during an additional 12-week treatment period. During the corticosteroid taper, the dose was reduced by approximately 25% of the baseline dose every 2 weeks for 8 weeks until discontinuation or worsening of asthma symptoms. The incidence of asthma exacerbations was reduced to a greater extent in the omalizumab-treated patients.

The incidence of asthma exacerbations per person was 0.28 in the omalizumab group and 0.54 in the placebo group ($P = 0.006$) during the stable corticosteroid phase and 0.39 in the omalizumab group and 0.66 in the placebo group ($P = .003$) during the corticosteroid taper. One or more exacerbation was experienced by 14.6% of omalizumab-treated patients and 23.3% of placebo-treated patients ($P = 0.009$) during the stable phase and 21.3% of omalizumab-treated patients and 32.3% of placebo-treated patients ($P = 0.004$) during the taper phase. Fewer patients in the omalizumab group had exacerbations requiring urgent, unscheduled physician visits (3% vs 7.4%) or were associated with a reduction in PEF to 50% or less of personal best value (0.4% vs 3.5%).

Beclomethasone dipropionate use was reduced by a median of 75% in the omalizumab group compared with 50% in the placebo group ($P < 0.001$) during the taper phase. Beclomethasone was discontinued during the taper phase in 39.6% of omalizumab-treated patients compared with 19.1% of placebo-treated patients ($P < 0.001$). Patients in the omalizumab group also had greater improvement in FEV_1 (68.2% to 72.53% vs 67.7% vs 69.1%, $P < 0.001$ to 0.19 over the course of the study), improved asthma scores, and reduced rescue medication use compared with those in the placebo group. Physicians rated treatment as good (marked improvement of asthma) or excellent (complete asthma control) for 53.1% of omalizumab recipients compared with 33.3% of placebo recipients ($P < 0.001$).[16]

Following the completion of the 28-week study, 460 patients entered a 24-week double-blind extension phase (245 in the omalizumab group and 215 in the placebo group). Quality of life was assessed at weeks 16 (end of the stable corticosteroid dosage phase), 28 weeks (end of the corticosteroid reduction phase), and 52 weeks (study completion). Improvements in all quality of life domains (activities, emotions, symptoms, and environmental exposure) were observed in the omalizumab group compared with the placebo group at each assessment.[17]

Omalizumab was also evaluated in a similar phase III double-blind, placebo-controlled study that enrolled 546 patients 12 to 76 years of age with moderate-to-severe asthma symptomatic despite daily inhaled corticosteroids. Patients were required to have positive immediate responses to skin-prick testing to at least one common allergen, total serum IgE levels of 30 international units/mL to 700 international units/mL, FEV1 reversibility of at least 12% within 30 minutes of albuterol administration, baseline FEV^1 between 40% and 80% of predicted, and treatment with 500 to 1200 mcg/day of beclomethasone dipropionate or its equivalent for at least 3 months prior to randomization.

Approximately 22% of patients met NHLBI criteria for severe persistent asthma; 78% met NHLBI criteria for moderate persistent asthma. Patients were switched to beclomethasone dipropionate if they were receiving an alternate corticosteroid, and maintained on a steady dose prior to randomization and the first 16 weeks of the study. Patients received either omalizumab (274 patients, dosed according to baseline total serum IgE and body weight) or placebo (272 patients) every 2 or 4 weeks SC for an initial 16-week period, while continuing inhaled corticosteroid use, then entered an 8-week phase during which inhaled corticosteroid use was reduced by 25% from baseline every 2 weeks if possible. For 4 weeks thereafter, patients remained on the lowest dose of inhaled corticosteroid required for asthma control.

During the first 16-week phase, there were 58% fewer mean exacerbations per patient in the omalizumab group compared with the placebo group ($P < 0.001$). During the steroid reduction phase, there were 52% fewer mean exacerbations per patient in the omalizumab group than in the placebo group ($P < 0.001$). The incidence of asthma

exacerbations per person was 0.28 in the omalizumab group and 0.66 in the placebo group ($P < 0.001$) during the stable corticosteroid phase and 0.36 in the omalizumab group and 0.75 in the placebo group ($P < 0.001$) during the corticosteroid taper. One or more exacerbations was experienced by 35% of omalizumab-treated patients and 83% of placebo-treated patients ($P < 0.001$) during the stable phase and 43% of omalizumab-treated patients and 81% of placebo-treated patients ($P < 0.001$) during the taper phase.

At the end of the study, omalizumab- treated patients had reduced their inhaled corticosteroid dose by a median of 75% to 83% from baseline, while those in the placebo group were able to reduce their inhaled corticosteroid dose by 50% ($P < 0.001$). Discontinuation of inhaled corticosteroids was achieved in 43% of omalizumab-treated patients compared with 19% of placebo-treated patients ($P < 0.001$).

A 50% reduction was achieved in 79% of omalizumab-treated patients, compared with 55% of placebo-treated patients ($P > 0.001$). FEV_1 and mean morning PEF demonstrated greater improvements in the omalizumab group during both the stable corticosteroid phase and the corticosteroid taper phase.[18,19] Following the completion of the 28-week study, 483 patients entered a 24-week, double-blind extension phase (254 in the omalizumab group and 229 in the placebo group). During the extension phase, patients were maintained on randomized treatment plus the lowest sustained dose of beclomethasone as established during the corticosteroids taper phase. The mean beclomethasone dipropionate dose during the extension was 253 mcg/day in the omalizumab group and 434 mcg/day in the placebo group. No asthma exacerbations occurred during the extension phase in 76% of the omalizumab-treated patients compared with 59.4% of the placebo-treated patients.[20]

Quality of life was assessed at 16 weeks (end of the stable corticosteroid dosage phase), 28 weeks (end of the corticosteroid reduction phase), and 52 weeks (study completion). Improvements in all quality of life domains (activities, emotions, symptoms, and environmental exposure) were observed in the omalizumab group compared with the placebo group at each assessment.[21]

The two previously described studies and a third study described in the product information formed the basis for FDA approval. The third study was also a randomized, double-blind, placebo-controlled study enrolling patients 12 to 76 years of age with moderate-to-severe asthma and a positive skin test reaction to a perennial allergen.

As in the other two studies, patients were symptomatic despite therapy with inhaled corticosteroids (at least 1000 mcg/day of fluticasone propionate); a subset of patients in this study was also receiving oral corticosteroids. Following a run-in period during which patients not previously on fluticasone were switched to a stable dose of this agent, patients were randomized to omalizumab or placebo. Therapy was continued with stable corticosteroid doses for 16 weeks, followed by a 16-week period during which corticosteroid doses were tapered. In this study, the percentage of patients with at least one asthma exacerbation was similar in the two treatment groups both during the stable corticosteroid phase and during the corticosteroid reduction phase.[1]

Omalizumab was also evaluated in a double-blind, placebo-controlled study that enrolled 317 patients 11 to 50 years of age with moderate-to-severe perennial allergic asthma requiring inhaled or oral corticosteroids. Patients were required to have a positive response to skin-prick testing to two or more perennial allergens to which the subjects would be exposed.

Following a 4-week run-in period, patients received either placebo or omalizumab 2.5 mcg/kg of body weight per nanogram of IgE per milliliter, or omalizumab 5.8 mcg/kg per nanogram of IgE per milliliter. Therapy was administered intravenously on days 0 (half dose), 4 (half dose), and 7 (full dose), and then once every 2 weeks thereafter for 20 weeks. For the first 12 weeks of the study, patients continued their corticosteroids as before study initiation, then for the next 8 weeks corticosteroid doses were tapered in an attempt to discontinue corticosteroid therapy.

The primary outcome measure was an improvement in the asthma symptom scores at 12 weeks, according to a 7-point scale in which a score of 1 indicated no symptoms and a score of 7 indicated the most severe symptoms. The mean asthma symptoms score was 4 at baseline. After 12 weeks of therapy, the mean scores were 2.8 in both the low-dose ($P = 0.005$) and high-dose groups ($P = 0.008$), compared with a score of 3.1 in the placebo group. At 20 weeks, the mean scores were 2.7 in both the low-dose ($P = 0.14$) and high-dose groups ($P = 0.048$), as compared with a score of 2.9 in the placebo group. A reduction in weekly symptom scores of more than 50% at week 12 occurred in 47% of patients in the low-dose group ($P < 0.001$), 49% of patients in the high-dose group ($P < 0.001$), and 24% of patients in the placebo group. Albuterol inhaler use was reduced by 1.8 puffs per day after 12 weeks in the high-dose group ($P = 0.02$), but was reduced by only 1.2 puffs per day in the low-dose group ($P = 0.24$) and 0.8 puffs per day in the placebo group.

More subjects in the omalizumab groups were able to decrease or discontinue corticosteroid use. Among patients on oral corticosteroids, 78% in the high-dose omalizumab group ($P = 0.04$) and 57% in the low-dose group ($P = 0.23$) had a reduction in dose of oral corticosteroids of at least 50%, compared with 33% of subjects in the placebo group. The dose of inhaled corticosteroids was reduced by at least 50% in 51% of patients in the high-dose group ($P = 0.07$), 49% in the low-dose group ($P = 0.12$), and 38% of patients in the placebo group.

The FEV1 improved to a similar extent in the three groups. Morning peak expiratory flow rate was increased from baseline by 29.9 L/min in the high-dose group ($P = 0.02$) and 20.8 L/min in the low-dose group ($P = 0.046$), compared to 10.2 L/min in the placebo group. Quality of life scores were improved in both omalizumab treatment groups compared to the placebo group.

Asthma exacerbation occurred in 32 patients in the high-dose group (30%, $P = 0.03$) and 30 patients in the low-dose group (28%, $P = 0.01$), compared with 47 patients in the placebo group (45%). After 20 weeks, serum free IgE concentration was reduced by a mean of more than 95% in both omalizumab groups. Free IgE concentrations declined rapidly after the first dose. In the high-dose group, serum free IgE concentrations fell from 1000 ng/mL to 7.3 ng/mL within 1 hour after the first dose. In the low-dose group, the serum free IgE fell from 1060 ng/mL to 13.9 ng/mL. After 20 weeks, the serum free IgE concentrations averaged 10.2 ng/mL in the high-dose group and 18 ng/mL in the low-dose group.[4]

In another similar study, omalizumab was compared with placebo in 334 children 6 to 12 years of age with moderate-to-severe asthma well controlled with inhaled corticosteroids and beta agonists. Enrollment criteria were similar to those in the studies described above.

During a run-in phase, all children were switched to a stable dose of inhaled beclomethasone dipropionate while maintaining control comparable to that achieved with their previous treatment. Patients were randomized to omalizumab at a dose based on body weight and total serum IgE (225 patients) or placebo (109 patients). For the first 16 weeks, patients received either omalizumab or placebo while continuing their stable inhaled corticosteroid dose. For the next 8 weeks, the inhaled corticosteroid was tapered by 25% every 2 weeks as tolerated, and then this minimum effective dose was maintained for an additional 4 weeks. The inhaled corticosteroid dose was reduced by a median of 100% in the omalizumab group compared with a 67% median reduction in the placebo group ($P = 0.001$). During the tapering period, 55% of omalizumab-treated patients and 39% of placebo-treated patients were able to completely discontinue inhaled corticosteroid therapy ($P = 0.004$).

The incidence of asthma exacerbations per patient was 0.42 in the omalizumab group and 0.72 in the placebo group ($P < 0.001$) during the corticosteroid taper. One or more exacerbations were experienced by 18.2% of omalizumab-treated patients and 38.5% of placebo-treated patients ($P < 0.001$) during the taper phase. At week 28, the mean number of doses of rescue medication taken daily was 0 in the omalizumab group compared with 0.46 in the placebo group.

Over the entire treatment period, patients in the omalizumab group missed a mean of 0.65 school days, while those in the placebo group missed a mean of 1.21 school days. The mean number of unscheduled medical contacts for asthma care was 0.15 in the omalizumab group compared with 5.35 in the placebo group. An urgent, unscheduled physician visit occurred in 30.3% of placebotreated patients compared with 12.9% of omalizumab-treated patients ($P = 0.001$). Treatment effectiveness was rated excellent by the investigators for 31.5% of omalizumab recipients compared with 16.3% of placebo recipients and good for 44.7% in the omalizumab group compared with 32.7% in the placebo group ($P < 0.001$).[22,23]

A Pediatric Asthma Quality of Life Questionnaire was administered at baseline, week 16, and week 28 of this study. At the end of the corticosteroid taper phase, patients in the omalizumab group reported improvement in the "activities" and "symptoms" domains of the assessment, as well as overall QOL scores.[24]

Omalizumab was also evaluated in a long-term evaluation. Omalizumab was compared with placebo in 546 patients (mean age 39.5 years) with moderate-to-severe asthma. Patients received either omalizumab or placebo for 52 weeks (7 months in a double-blind, placebo-controlled study with a 5-month blinded extension phase). Therapy was rated as excellent (complete control of asthma) or good (marked improvement of asthma) by approximately 70% of patients treated with omalizumab compared to 42.6% of placebotreated patients ($P < 0.001$).

Therapy was rated as excellent by 26% of omalizumab-treated patients compared with 8.1% of placebo-treated patients, good by 43.5% of omalizumab-treated patients and 34.5% of placebo-treated patients, moderate (discernible, but limited improvement in asthma) by 19.8% of omalizumab-treated patients and 30.6% of placebo-treated patients, poor (no appreciable change in asthma) by 8.4% of omalizumab-treated patients and 21.7% of placebo-treated patients, and worse by 2.3% of omalizumab-treated patients and 5% of placebo-treated patients. Investigators rated omalizumab therapy as excellent or good for 66% of patients.[25]

Allergic Rhinitis (Non-FDA-Approved Indication)

The efficacy of omalizumab was also assessed in the treatment of ragweed-induced allergic rhinitis in a double-blind, placebo-controlled trial enrolling 240 patients with documented history of seasonal allergic rhinitis or rhinoconjunctivitis and well-characterized positive reactivity to ragweed allergen. Placebo or omalizumab was administered on days 0, 7, 14, 28, 42, 56, 70, and 84. Subjects were assigned one of five treatment arms: (1) placebo IV and SC on day 0 followed by placebo SC for subsequent doses (20 patients); (2) omalizumab 0.15 mg /kg IV and SC on day 0 followed by omalizumab 0.15 mg/kg SC for the subsequent doses (60 patients); (3) omalizumab 0.3 mg/kg IV on day 0 followed by omalizumab 0.15 mg/kg IV for subsequent doses (60 patients); (4) omalizumab 0.5 mg/kg IV on day 0 followed by omalizumab 0.5 mg/kg IV for subsequent doses; and (5) placebo IV on day 0 followed by placebo IV for subsequent doses.

Patients received no other therapy for allergic rhinitis throughout the study, although rescue medication (clemastine fumarate 1.34 mg, phenylpropanolamine HCl 75 mg sustained-release tablets) was available for relief of allergic rhinitis symptoms scored as 2 or more on a daily diary score card.

Serum free IgE was reduced in a dose-dependent manner. In the 0.15 mg/kg SC and IV groups, serum concentrations of free IgE at steady-state were approximately 60% of

baseline free IgE, with no difference in pharmacodynamics between the SC and IV routes of administration. In the 0.5 mg/kg IV group, serum concentrations of free IgE at steady-state were approximately 30% of baseline. Total serum IgE and ragweed-specific total IgE increased 2- to 3-fold in the 0.15 SC and IV groups and by 4- to 5-fold in the 0.5 mg/kg IV group.

The average daily symptom score of patients receiving placebo was slightly higher than that of patients treated with omalizumab, but the difference was not statistically significant. The average symptom score during the season was 0.91 for placebo-treated patients and 0.73 to 0.82 for omalizumab-treated patients. At the peak of the season, when pollen counts were highest, the average symptom scores were only 1 for placebo-treated patients and 0.8 to 0.9 for omalizumab-treated patients. The use of rescue medication did not differ between placebo and omalizumab groups. No significant effect on quality-of-life scores was observed. Skin test reactivity did not change in the placebo and omalizumab 0.15 mg/kg dose groups, although an increase in the concentration of ragweed allergen needed to obtain the standard response was increased slightly in the omalizumab 0.5 mg/kg group. Omalizumab is able to decrease symptoms when the serum free IgE concentration is significantly reduced.[14]

Another similar study assessed the efficacy of omalizumab in seasonal allergic rhinitis at higher doses predicted to reduce serum free IgE levels below 25 ng/mL. The double-blind, placebo-controlled study enrolled 251 adult patients with a history of seasonal allergic rhinitis and a positive skin test response to birch pollen. Subjects received either placebo or omalizumab 300 mg.

Therapy was administered two or three times during the birch pollen season, depending on the patient's baseline IgE level. Patients with baseline serum IgE levels of 150 international units/mL or less received omalizumab 300 mg SC or placebo at week 0 and week 4; patients with baseline serum IgE levels greater than 150 international units/mL received 300 mg of omalizumab SC or placebo at weeks 0, 3, and 6. Antihistamine rescue medication (acrivastine, dexchlorpheniramine, or loratadine) was permitted.

The average daily nasal symptom severity score in the omalizumab group was similar at baseline and throughout the treatment period, with mean values of 0.71 at baseline and 0.7 during treatment. In the placebo group, the average daily nasal symptom severity score increased from 0.78 at baseline to 0.98 during treatment ($P < 0.001$). The average daily ocular symptom severity score decreased from 0.47 at baseline to 0.43 during treatment in the omalizumab group and increased from 0.43 at baseline to 0.54 during treatment in the placebo group ($P = 0.031$).

Rescue antihistamine use was reduced in the omalizumab group compared with the placebo group (0.59 tablets/day vs 1.37 tablets/day, $P < 0.001$). Rescue medication was used on 49% of days in the placebo group compared with 28% of days in the omalizumab group ($P < 0.001$). Quality-of-life scores favored omalizumab with regard to total score, and the domains of activities, nasal symptoms, non nose–eye symptoms, and practical problems. Complete control of symptoms was reported by 21% of omalizumab-treated patients compared with 2% of placebo-treated patients. Improvement was reported by another 59% of omalizumab-treated patients compared with 35% of placebo-treated patients. Serum free IgE levels at weeks 3 or 4 were below 25 ng/mL in 69% of subjects in the omalizumab group, but exceeded 50 ng/mL in all but one placebo-treated patient. Better clinical outcomes were observed in subjects with serum free IgE levels below 25 ng/mL compared with those with higher free IgE levels (see Table 1).[26]

Another double-blind study assessed omalizumab compared with placebo for the prevention of symptoms

Table 1: Correlation Between Clinical Efficacy and Serum Free IgE Concentration in Patients Treated with Omalizumab for Seasonal Allergic Rhinitis[26]

Efficacy Variable	Serum Free IgE Level	Numbers of Patients	Mean	Least Square Means Difference (SE) Relative to Group 4	P Value Relative to Group 4
Average daily nasal symptom severity score	(1) ≤ 25 ng/mL	113	0.68	–0.37 (0.08)	< 0.001
	(2) > 25–50 ng/mL	48	0.77	–0.25 (0.1)	0.01
	(3) > 50–150 ng/mL	33	0.86	–0.20 (0.11)	0.056
	(4) > 150 ng/mL	54	1.03		
Average daily number of tablets of rescue antihistamine	(1) ≤ 25 ng/mL	113	0.46	–1.07 (0.18)	< 0.001
	(2) > 25–50 ng/mL	49	0.58	–0.84 (0.21)	< 0.001
	(3) > 50–150 ng/mL	33	0.87	–0.64 (0.24)	0.008
	(4) > 150 ng/mL	54	1.49		
Proportion of days with seasonal allergic rhinitis medication use	(1) ≤ 25 ng/mL	113	0.22	–0.27 (0.05)	< 0.001
	(2) > 25–50 ng/mL	48	0.27	–0.22 (0.06)	< 0.001
	(3) > 50–150 ng/mL	33	0.37	–0.13 (0.06)	0.041
	(4) > 150 ng/mL	54	0.49		

in 536 patients 12 to 75 years of age with seasonal allergic rhinitis. Patients with at least a 2- year history of moderate-to-severe ragweed-induced seasonal allergic rhinitis and a baseline IgE levels between 30 and 700 international units/mL were randomized to therapy with omalizumab 50 mg (137 patients), 150 mg (134 patients), or 300 mg (129 patients), or placebo (136 patients) administered SC just prior to ragweed season and repeated during the pollen season every 3 weeks in patients with baseline IgE levels of 151 to 700 international units/mL (4 doses total) and every 4 weeks in patients with baseline IgE levels of 30 to 150 international units/mL (3 doses total).

Nasal symptom severity scores were lower in patients treated with omalizumab 300 mg than those treated with placebo (0.75 vs 0.98, $P = 0.002$), as were ocular symptom severity scores (0.41 vs 0.67, $P = 0.001$) and overall symptom severity scores (0.61 vs 0.85, $P < 0.001$). Ocular symptom severity and overall symptom severity were also reduced in the omalizumab group compared with the placebo group (ocular 0.45 vs 0.67; $P = 0.002$) and overall (0.68 vs 0.85; $P = 0.009$). The proportion of days with rescue antihistamine or concomitant medication use was lower in the omalizumab 300 mg (0.12 vs 0.21 days with placebo; $P = 0.005$) and 150 mg (0.13 vs 0.21 days with placebo; $P = 0.01$) groups.

An association was observed between IgE reduction and nasal symptoms and rescue antihistamine use. Patients with the lowest free IgE levels had the lowest symptom scores and the least frequent rescue antihistamine use. A free IgE level less than 10.4 international units/mL was achieved in 63% of patients in the 300 mg group, 33% in the 150 mg group, 4% in the 50 mg group, and 3% in the placebo group. Treatment was globally rated good or excellent by 70% in the 300 mg group ($P < 0.001$), 60% in the 150 mg group ($P < 0.001$), 51.9% in the 50 mg group ($P = 0.007$), and 40.8% in the placebo group. The investigators rated therapy good or excellent for 65.3% in the 300 mg group ($P < 0.001$), 51.9% in the 150 mg group ($P = 0.001$), and 50% in the 50 mg group ($P = 0.004$) compared with 35.4% in the placebo group. Rhinitis specific quality of life scores were better in patients treated with omalizumab 300 mg than in those treated with placebo and did not decline during peak season.[27]

Contraindications, Warnings, and Precautions

Omalizumab is contraindicated in patients with a history of severe hypersensitivity reaction to omalizumab.[1]

Anaphylaxis occurred within 2 hours of the first or subsequent dose of omalizumab in three patients (less than 0.1% of patients) without other identifiable allergic triggers. Symptoms included urticaria and throat and/or tongue edema. Patients should be observed following omalizumab injection and medications for the treatment of severe hypersensitivity reactions should be available.[1] Omalizumab does not alleviate asthma exacerbations acutely and should not be used for the treatment of acute bronchospasm or status asthmaticus.[1] Patients should be advised that they may not see immediate improvement in their asthma upon initiation of omalizumab therapy.[1]

Systemic or inhaled corticosteroids should not be abruptly discontinued upon initiation of omalizumab therapy. A gradual reduction in dosage may be possible. Patients should be instructed to only decrease the dose of, or discontinue, other asthma medications if instructed by their prescriber.[1]

Malignant neoplasms were observed in 0.5% of omalizumabtreated patients (20/4127) and 0.2% of control patients (5/2236) in clinical trials. Malignancies were of a variety of types and a relationship to omalizumab was not established. The impact of longer exposure or use in patients at high risk for malignancy is not known.[1]

The safety and effectiveness of omalizumab have not been established in children under 12 years of age.[1]

Omalizumab is in Pregnancy Category B. Maternal toxicity, embryotoxicity, teratogenicity, or adverse effects on fetal or neonatal growth have not been observed in animal models. IgG molecules do cross the placental barrier. Omalizumab should be used during pregnancy only if clearly needed.[1]

Omalizumab is excreted in breast milk. In cynomolgus monkeys, neonatal plasma levels of omalizumab after *in utero* exposure and 28 days of nursing were between 11% and 94% of maternal plasma levels. Milk levels were 1.5% of maternal blood concentrations. Omalizumab excretion has not been assessed in human milk; however, because IgG is excreted in human milk, omalizumab is also expected to be present in human milk. The potential for omalizumab absorption or harm to the infant are unknown; therefore, caution is advised if omalizumab is administered to a nursing woman.[1]

Adverse Reactions

The most common adverse effects observed in studies of omalizumab in patients with asthma included injection site reactions, viral infections, upper respiratory tract infections, sinusitis, headaches, and pharyngitis, all of which occurred with similar frequency in omalizumab-treated and control patients.[1] Injection site reactions occurred in 45% of omalizumabtreated patients and 43% of placebo-treated patients. Types of injection reactions included bruising, redness, warmth, burning, stinging, itching, hives, pain, indurations, mass, and inflammation. Most reactions occurred within 1 hour after injection, lasted fewer than 8 days, and occurred with declining frequency with subsequent doses.[1]

In allergic rhinitis studies, headaches, infection, pain, and pharyngitis occurred frequently, but at a similar incidence in the omalizumab and placebo groups and probably reflected common symptoms of the condition being treated.[14] Injection site reactions also occurred with similar frequency in the omalizumab and placebo groups.[26]

Urticaria, generally occurring within 60 minutes after the infusion on the first day of treatment, has been reported in several patients.[4,9,26] Increased cough was reported in one patient shortly after omalizumab administration.[14]

Low titers of antibodies to omalizumab were detected in 1 of 1723 patients (< 0.1%) treated with omalizumab in

clinical trials.[1] Antibodies to omalizumab were not observed in several studies.[4,9,14] It is not clear if the low observed incidence of antibody formation truly reflects a low incidence of antibody formation or assay-related factors (sensitivity and specificity of the assay, sample handling, timing of sample collection, concomitant medications, and underlying diseases).[1]

Drug Interactions

Formal drug interaction studies with omalizumab have not been conducted.[1]

The concomitant use of omalizumab and allergen immunotherapy in the treatment of patients with allergic asthma has not been assessed.[1] In a study enrolling 225 children 6 to 17 years of age, omalizumab plus specific immunotherapy produced a greater reduction in symptoms than immunotherapy alone.[28]

Recommended Monitoring

Baseline serum total IgE levels are necessary to determine the appropriate dose of omalizumab.

Dosing

The recommended dose of omalizumab is 150 to 375 mg administered SC every 2 or 4 weeks. Doses and dosage frequency are determined by serum total IgE levels measured prior to initiation of therapy and body weight. Table 2 contains doses for administration of omalizumab every 2 or 4 weeks based on body weight and pretreatment serum IgE.[1] Doses should be adjusted for major changes in body weight. Because total IgE levels are elevated during therapy and for up to 1 year afterward, retesting of serum IgE cannot be used to guide dosing decisions. If therapy is interrupted and restarted within a year of interruption, the original pretreatment serum IgE level should be used for dosage determination.[1]

Doses of more than 150 mg are divided among more than one injection site. A 150 mg dose requires one 1.2 mL injection; a 225 mg dose requires one 1.2 mL (150 mg) injection and one 0.6 mL (75 mg) injection; a 300 mg dose requires two 1.2 mL (150 mg) injections; and a 375 mg dose requires two 1.2 mL (150 mg) injections and one 0.6 mL (75 mg) injection. Because the solution is slightly viscous, an injection may take 5 to 10 seconds to administer.[1]

Product Availability

Omalizumab received FDA approval in June 2003. It is available as a sterile, preservative-free, lyophilized powder in a single-use vial. Each vial contains omalizumab 202.5 mg, sucrose 145.5 mg, Lhistidine hydrochloride monohydrate 2.8 mg, L-histidine 1.8 mg, and polysorbate 20 0.5 mg.[1] The product is shipped at ambient temperatures (≤ 30°C [≤ 86°F]), but should be stored under refrigeration at 2° to 8°C (36° to 46°F).[1]

Following reconstitution with 1.4 mL Sterile Water for Injection, USP, the vial contains omalizumab 150 mg in 1.2 mL. The lyophilized powder takes 15 to 20 minutes or longer to dissolve. The vial should be used within 8 hours of reconstitution if stored in the vial at 2° to 8°C (36° to 46°F) or within 4 hours if stored at room temperature.[1]

Conclusion

Omalizumab use should be reserved for patients with moderate-to-severe persistent allergic asthma with symptoms despite the use of inhaled corticosteroids. Patients must have a significant allergic component to their disease (elevated IgE levels, positive skin-prick test to a perennial allergen). In this population, omalizumab therapy has been associated with reduced asthma exacerbations and improved quality of life. Reducing the incidence of exacerbations may in turn reduce unscheduled health care visits, hospitalizations, and overall health care expenditures. Pharmacoeconomic analysis and future outcome studies will be useful to determine where this agent produces the greatest impact.

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Table 2. Omalizumab Doses Based on body Weight and Pretreatment IGE

Pretreatment Serum IgE (IU/mL)	Body Weight (kg)			
	30 – 60	> 60 – 70	> 70 – 90	> 90 – 150
> 30–100	150 mg every 4 wks	150 mg every 4 wks	150 mg every 4 wks	300 mg every 4 wks
> 100–200	300 mg every 4 wks	300 mg every 4 wks	300 mg every 4 wks	225 mg every 2 wks
> 200–300	300 mg every 4 wks	225 mg every 2 wks	225 mg every 2 wks	300 mg every 2 wks
> 300–400	225 mg every 2 wks	225 mg every 2 wks	300 mg every 2 wks	Do not dose
> 400–500	300 mg every 2 wks	300 mg every 2 wks	375 mg every 2 wks	Do not dose
> 500–600	300 mg every 2 wks	375 mg every 2 wks	Do not dose	Do not dose
> 600–700	375 mg every 2 wks	Do not dose	Do not dose	Do not dose

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Selected FDA Safety Alerts

Advair Diskus (fluticasone propionate and salmeterol inhalation powder)
Serevent Inhalation Aerosol (salmeterol xinafoate)
Serevent Diskus (salmeterol xinafoate inhalation powder)

The FDA announced the addition of new safety information and warnings to the labeling for drug products that contain salmeterol, a long-acting bronchodilator used to treat asthma and chronic obstructive pulmonary disease (COPD). The new labeling includes a boxed warning about a small, but significant, increased risk of life-threatening asthma episodes or asthma-related deaths observed in patients taking salmeterol in a recently completed large U.S. safety study.

Genotropin (somatropin [rDNA origin] for injection)

Pharmacia and FDA revised the CONTRAINDICATIONS and WARNINGS sections of the prescribing information for Genotropin, indicated for the long-term treatment of pediatric patients who have growth failure. Fatalities have been reported with the use of growth hormone in pediatric patients with Prader-Willi syndrome with one or more of the following risk factors: severe obesity, history of respiratory impairment or sleep apnea, or unidentified respiratory infection. Male patients with these factors may be at increased risk.

Lariam (mefloquine hydrochloride)

FDA and Roche Laboratories notified healthcare professionals of the introduction of the Lariam Medication Guide (MedGuide). The Lariam MedGuide was developed in collaboration with the FDA to help travelers better understand the risks of malaria, the risks and benefits associated with taking Lariam to prevent malaria, and the rare but potentially serious psychiatric adverse events associated with use of the drug. As required by law, a Lariam Medication Guide is supplied to patients each time Lariam is dispensed. Patients should be instructed to read the MedGuide when Lariam is received.

Prandin (repaglinide)

Novo Nordisk and FDA revised the PRECAUTIONS/ Drug Interaction section of the prescribing information to inform healthcare professionals of a drug-drug interaction between repaglinide (PRANDIN), a short-acting insulin secretagogue, and gemfibrozil (Lopid) a lipid-lowering agent used to treat dyslipidemia. A study that evaluated the co-administration of gemfibrozil with PRANDIN in healthy subjects found a significant increase in repaglinide blood levels. Concomitant use may result in enhanced and prolonged blood glucose-lowering effects of repaglinide. For patients already on PRANDIN and gemfibrozil, blood glucose levels should be monitored and PRANDIN dose adjustment may be needed.

Public Health Advisory – Suicidality in Pediatric Patients Treated with Antidepressants for Major Depressive Disorder

The FDA notified healthcare professionals of reports of the occurrence of suicidality (both suicidal ideation and suicide attempts) in clinical trials for various antidepressant drugs in pediatric patients with major depressive disorder (MDD). FDA has completed a preliminary review of such reports for eight antidepressant drugs (citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, and venlafaxine) studied under the pediatric exclusivity provision, and has determined that additional data and analysis, and also a public discussion of available data, are needed. FDA plans to hold an advisory committee meeting before the Psychopharmacologic Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee on February 2, 2004.

Pyrazinamide plus Rifampin for Treatment of Latent Tuberculosis Infection (LTBI)

The Centers for Disease Control and Prevention (CDC) notified healthcare professionals of revised recommendations against the use of rifampin plus pyrazinamide for treatment of latent tuberculosis infection, due to high rates of hospitalization and death from liver injury associated with the combined use of these drugs.

Reyataz (atazanavir sulfate)

BMS and FDA notified clinicians caring for HIV-infected patients of important new safety data concerning the coadministration of Reyataz (atazanavir sulfate) and Viread (tenofovir disoproxil fumarate.) Clinicians should use caution when administering unboosted Reyataz with tenofovir DF. Unboosted Reyataz may be less effective due to decreased atazanavir concentrations in patients taking Reyataz and tenofovir DF. As a result the coadministration of unboosted Reyataz with tenofovir DF may lead to loss or lack of virologic response and possible resistance to Reyataz.

Topamax (topiramate) Tablets/Sprinkle Capsules

Ortho-McNeil and FDA revised the WARNINGS and PRECAUTIONS sections of the prescribing information to provide updated information about oligohidrosis (decreased sweating) and hyperthermia, which have been reported in topiramate-treated patients. Oligohidrosis and hyperthermia may have potentially serious sequelae, which may be preventable by prompt recognition of symptoms and appropriate treatment.

Valcyte (valganciclovir HCl tablets)

FDA and Roche notified healthcare professionals of the findings of an active comparator study of Valcyte and ganciclovir in heart, liver, kidney, and kidney-pancreas transplant patients at high risk for CMV disease. Based on those findings: (1) Valcyte is indicated for the prevention of CMV disease in kidney, heart, and kidney-pancreas transplant patients at high risk, (2) Valcyte is not indicated for use in liver transplant patients, and (3) The safety and efficacy of Valcyte for the prevention of CMV disease in other solid organ transplant patients, such as lung transplant patients, have not been established.

Viread (tenofovir disoproxil fumarate)

Gilead Sciences, Inc. notified healthcare professionals of a high rate of early virologic failure and emergence of nucleoside reverse transcriptase inhibitor (NRTI) resistance associated mutations observed in a clinical study of HIV-infected treatment-naïve patients receiving a once-daily triple NRTI regimen containing didanosine enteric coated beadlets (Videx EC, Bristol-Myers Squibb), lamivudine (Epivir, GlaxoSmithKline), and tenofovir disoproxil fumarate (Viread, Gilead). Based on these results, Tenofovir DF in combination with didanosine and lamivudine is not recommended when considering a new treatment regimen for therapy-naïve or experienced patients with HIV infection. Patients currently on this regimen should be considered for treatment modification.

Ziagen (abacavir)

GlaxoSmithKline (GSK) notified healthcare professionals of a high rate of early virologic non-response observed in a GSK-sponsored clinical study of therapy-naive adults with HIV infection receiving once-daily three-drug combination therapy with lamivudine (Epivir, GSK), abacavir (Ziagen, GSK) and tenofovir (Viread, TDF, Gilead Sciences). Based on these results: Abacavir and lamivudine in combination with tenofovir should not be used as a triple antiretroviral therapy when considering a new treatment regimen for naive or pre-treated patients.

Note: **Detailed information on these and other FDA safety alerts is available via the FDA homepage (*www.fda.gov*).**

Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary changes:

Additions

- Omalizumab (Xolair), an injectable anti-IgE antibody for the treatment of moderate-to-severe persistent allergic asthma

Deletions

None

FDA Safety Alerts

- You can access the latest safety information from the Food and Drug Administration website. To access "Dear Health Professional" letters, other safety notifications, and labeling changes related to drug safety, just point your browser to *www.fda.gov* and click on "MedWatch." MedWatch is the FDA's medical products reporting program.

- You can receive immediate e-mail notification of new material as soon as it is posted on the MedWatch website. Just send a subscription message to *fdalists@archie.fda.gov.* In the message body enter: *subscribe medwatch* and your e-mail address.

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