UP TO DATE

Omalizumab. A review of the new treatment of allergic asthma and seasonal allergic rhinitis

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SUMMARY

The causal role of immunoglobulin E (IgE) in triggering the cascade of biochemical events leading to allergic disease is well established. Treatments that selectively inhibit IgE activity are a logical approach in managing the allergic response. Omalizumab is a recombinant humanised monoclonal antibody which specifically binds to the Cϵ3 domain of immunoglobulin (Ig) E, the site of high-affinity IgE receptor binding. The clinical benefit and steroid-sparing effect of treatment with the anti-immunoglobulin-E (IgE) antibody, Omalizumab, was assessed in patients with moderate-to-severe allergic asthma and seasonal allergic rhinitis. Intravenous and subcutaneous administration of anti-IgE mAb reduces circulating levels of IgE in atopic patients to low levels commonly seen in non-atopic individuals. Anti-IgE therapy offers protection against allergen-induced bronchoconstriction, reduces the need for short acting inhaled beta 2-agonist and corticosteroids among asthmatic patients and reduces severity of symptoms of allergic rhinitis. Adverse events were infrequent in clinical trials of omalizumab, and not significantly different from placebo. The most frequent drug-related event was mild to moderate urticaria. They do not induce anaphylaxis and the occurrence of antibodies against anti-IgE mAb is sporadic. The results of cited studies suggest that humanized anti-IgE monoclonal antibodies may have important immunotherapeutic benefit for treatment of allergic disorders.

Key words: Omalizumab. RhuMAb-E25. Anti-IgE. Asthma. Rhinitis.

INTRODUCTION

Allergic diseases are characterized by biphasic reactions mediated by IgE (1). The immediate reaction appears within minutes after exposure to an antigen, and the late-phase reaction may occur two to eight hours afterward. The latter process is the model for allergic disease (2, 3). Lung biopsy (4, 5) and bronchoalveolar lavage (6) in subjects with stable asthma show the presence of inflammation consistent with a late-phase reaction, whereas pulmonary-function tests show hyperresponsiveness of the airway that is proportional to the magnitude of the late-phase reaction (7). IgE binds to high-affinity receptors on tissue mast cells and circulating basophils (8). In subjects with asthma, there is a correlation between serum IgE concentrations and both airway responsiveness (9) and the number of high-affinity receptors.

Effective allergen immunotherapy attenuates the late-phase reaction (10). However, immunotherapy as currently practiced has not been uniformly effective in the treatment of allergic disease (11, 12). Consequently, in some patients the basis of therapy remains the consistent use of antiinflammatory medication, most often in the form of inhaled corticosteroids, to block the late-phase reaction and reduce airway hyperresponsiveness (13). Successful antiinflammatory therapy leads to long-term prevention of the symptoms of asthma by suppressing, controlling, and reversing inflammation (14). The clinical efficacy of rhuMAb-E25 may be the

result of similar effects on the pathogenesis of the allergic response.

Although immunotherapy is effective only in a narrow, antigen-specific range, rhuMAb-E25 removes IgE from the circulation, basophils (15, 16), and mast cells regardless of its antigen specificity.

MONOCLONAL ANTI-IGE ANTIBODY

Recombinant humanized monoclonal antibody (rhuMAb-E25) was developed by immunizing mice with human IgE. A monoclonal antibody was selected that recognizes IgE at the same site as the high-affinity receptor for IgE (FcϵRI) (17). This antibody forms complexes with free (unbound) IgE but not with IgG or IgA. It blocks the binding of IgE to cell-membrane receptors, thereby inhibiting the release of mediators, but it does not bind to cell-bound IgE (18). For clinical use, the amino acid residues of the variable immunoglobulin region of mouse origin that were implicated in binding to IgE were grafted onto the constant region of human IgG1, resulting in an immunoglobulin protein that is more than 95 percent human (19). The use of rhuMAb-E25 dramatically reduces serum concentrations of free IgE immediately after the first injection (20) and, after a course of therapy, attenuates both early- and late-phase reactions to inhaled allergens (21, 22). A single dose of rhuMAb-E25 rapidly reduced serum free IgE serum concentrations by more than 95 percent, and correlate with improvements in clinical outcomes. Although serum free IgE concentrations declined precipitously, mean serum total IgE concentrations, consisting mostly of immunoglobulin complexes, increased over time and appeared to reach a plateau. The ability of rhuMAb-E25 to suppress the late-phase reaction, which is associated with bronchial inflammation followed by bronchoconstriction, has been postulated to have a beneficial effect on the pathogenesis of asthma (23).

Eosinophil and neutrophil numbers in induced sputum and blood eosinophil levels were not significantly different from placebo (24).

Analytic ultracentrifugation and size-exclusion chromatography identified the largest complexes of rhuMAb-E25 and IgE as heterohexamers with a molecular mass of 1,000,000 or less (25). Because these complexes cannot bind IgE receptors, they lack the biologic activity of IgE. The complexes are cleared by low-avidity interaction with the Fcϵ receptors of leukocytes and the reticuloendothelial system (20). These low-molecular-weight complexes, which do not fix complement or accumulate in renal glomeruli, do not pose a risk of immunopathogenicity (20). Omalizumab was cleared slowly from circulation with a terminal elimination half-life of 1 to 4 weeks.

In the last years, omalizumab has been reviewed in numerous studies (26-32) and there are so many clinical trials (35-43). We reviewed and present next the most important of them and their results.

CLINICAL TRIALS

The therapeutic efficacy of Omalizumab (rhu-Mab-E25) has been evaluated in multicentre, randomised, double-blind, placebo controlled, parallel-group studies in children, adolescents and adults with allergic asthma, and in adolescents and adults with seasonal allergic rhinitis.

Allergic asthma

Milgrom et al (33) studied the efficacy of rhuMAb-E25 as a treatment for moderate-to-severe allergic asthma. After a 4-week run-in period, they randomly assigned 317 subjects (age range, 11 to 50 years) who required inhaled or oral corticosteroids (or both) to receive either placebo or one of two regimens of rhuMAB-E25: high-dose rhuMAb-E25 (5.8 microg per kilogram of body weight per nanogram of IgE per milliliter or low-dose rhuMAb-E25 (2.5 microg per kilogram per nanogram of IgE per milliliter) intravenously on days 0 (half a dose), 4 (half a dose), and 7 (full dose) and then once every 2 weeks thereafter for 20 weeks. For the first 12 weeks of the study, the subjects continued the regimen of corticosteroids they had received before enrollment. During the following eight weeks, the doses of corticosteroids were tapered in an effort to discontinue this therapy. The primary outcomes were daytime and nocturnal 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 the most severe symptoms. The secondary outcomes were changes in the extent of use of a β-agonist bronchodilator as a rescue medication, the doses of oral and inhaled corticosteroids, peak expiratory flow rate, and asthma-specific quality of life. A total of 106 subjects were assigned to receive a high dose of rhuMAb-E25, 106 were assigned to receive a low dose, and 105 were assigned to receive placebo. At base line, the mean asthma symptom score was 4.0. After 12 weeks of therapy,

the mean (± SE) scores were 2.8 ± 0.1 in the high-dose group (p = 0.008) and 2.8 ± 0.1 in the low-dose group (P = 0.005), as compared with 3.8 ± 0.1 in the placebo group. At 20 weeks, the mean scores were 2.7 ± 0.1 in both the high-dose group (p = 0.048) and the low-dose group (P = 0.14), as compared with 2.9 ± 0.1 in the placebo group. During the 20 weeks of treatment, 32 subjects in the high-dose group (30 percent, p = 0.03) and 30 subjects in the low-dose group (28 percent, p = 0.01) had exacerbations of asthma, as compared with 47 subjects in the placebo group (45 percent). More subjects in the two rhuMAb-E25 groups were able to decrease or discontinue their use of corticosteroids than in the placebo group. After the 20 weeks, serum free IgE concentrations decreased by a mean of more than 95 percent in both rhuMAb-E25 groups. The therapy was well tolerated. There were 17 reports of mild-to-moderate urticaria (8 in the high-dose group, 6 in the low-dose group, and 3 in the placebo group). Ten cases occurred within 60 minutes after the infusion on the first day of treatment (three in the low-dose group and seven in the high-dose group), and all subsided promptly after treatment with antihistamines. After 20 weeks, none of the subjects had antibodies against rhuMAb-E25.

Recently, Milgrom et al (34) studied this treatment in children with moderate to severe allergic asthma. They report that nearly 90 % of affected children have positive skin tests indicating the presence of specific immunoglobulin E (IgE), with sensitivity to house dust mite, Alternaria, cockroach, cat, and dog most closely linked to the disease. Greater exposure to house dust mite during infancy leads to earlier onset of wheezing, and elevated serum IgE levels correlate with the appearance of asthma symptoms. This double-blind, randomized, placebo-controlled study evaluated the safety, steroid-sparing effects, and impact on disease exacerbations of omalizumab in 334 males and premenarchal females aged 6 to 12 years, with moderate to severe allergic asthma requiring treatment with inhaled corticosteroids. During a run-in phase, all children were switched to equivalent doses of beclomethasone dipropionate (BDP), and the dose was adjusted to assure maintenance of asthma control achieved with previous corticosteroid treatment. Children were randomized to subcutaneously administered placebo (N = 109) or omalizumab (N = 225) at a dose based on body weight and initial serum IgE (0.016 mg/kg/IgE [IU/mL] per 4 weeks). BDP dose was kept stable for 16 weeks (stable-steroid phase), reduced over 8 weeks to the minimum effective dose (steroid-reduction phase), and maintained constant for the final 4 weeks. They report that more

participants in the omalizumab group decreased their BDP dose, and their reduction was greater than that of the placebo group (median reduction 100 % vs 66.7 %). BDP was withdrawn completely in 55 % of the omalizumab group versus 39 % of the placebo group. The incidence and the frequency of asthma exacerbations requiring treatment with doubling of BDP dose or systemic corticosteroids were lower in the omalizumab group. The treatment differences were statistically significant during the steroid-reduction phase, during which fewer participants in the omalizumab group had asthma exacerbation episodes (18.2 % vs 38.5 %), and the mean number of episodes per patient was smaller than with placebo (0.42 vs 2.72). Five asthma exacerbations requiring hospitalization all occurred in the placebo group. Participants' and investigators' global evaluations of treatment effectiveness were more favorable for omalizumab than placebo. Investigators rated effectiveness excellent for 31.5 % of the omalizumab group versus 16.3 % of the placebo group and good for 44.7 % of the omalizumab group versus 32.7 % of the placebo group. There was little change in asthma symptom scores or spirometry measurements during either the stable-steroid or steroid dose-reduction phase, with minimal differences between the treatment groups. The requirement for rescue medication in the omalizumab group during both the stable-steroid and steroid dose-reduction phases was consistently lower than at baseline. At week 28, the median number of puffs of rescue medication taken daily was 0 in the omalizumab group and 0.46 in the placebo group. The change from baseline was significant in favor of omalizumab. Median reduction in serum free IgE was 95 % to 99 % among omalizumab patients. Median free IgE ranged from 133 to 790 IU/mL at baseline and was in the range of 6 to 9 IU/mL during the treatment period. The dosing scheme used in the trial therefore effectively reduced serum IgE in patients with initial concentrations as high as 1,300 IU/mL. There was no reduction in free IgE in the placebo group. Omalizumab treatment was well tolerated. There were no serious treatment-related adverse events. The frequency and types of all adverse events were similar in the omalizumab and placebo groups. The majority of adverse events were mild to moderate in severity.

Soler et al (35) studied 546 allergic asthmatics (aged 12-76 yrs), symptomatic despite inhaled corticosteroids (500-1,200 microg daily of beclomethasone dipropionate), who were randomized to receive double-blind either placebo or omalizumab every 2 or 4 weeks (depending on body weight and serum total IgE) subcutaneously for

7 months. A constant beclomethasone dose was maintained during a 16-week stable-steroid phase and progressively reduced to the lowest dose required for asthma control over the following 8 weeks. The latter dose was maintained for the next 4 weeks. Asthma exacerbations represented the primary variable. Compared to the placebo group, the omalizumab group showed 58 % fewer exacerbations per patient during the stable-steroid phase (p < 0.001). During the steroid-reduction phase, there were 52 % fewer exacerbations in the omalizumab group versus the placebo group (p < 0.001) despite the greater reduction of the beclomethasone dosage on omalizumab (p < 0.001). Treatment with omalizumab was well tolerated. The incidence of adverse events was similar in both groups.

Busse et al (36), in a phase III, double-blinded, placebo-controlled trial, studied 525 subjects with severe allergic asthma who required daily inhaled corticosteroids, and were randomized to receive placebo or omalizumab subcutaneously every 2 or 4 weeks, depending on baseline IgE level and body weight. Inhaled corticosteroid doses were kept stable over the initial 16 weeks of treatment and tapered during a further 12 week treatment period. Omalizumab treatment resulted in significantly fewer asthma exacerbations per subject and in lower percentages of subjects experiencing an exacerbation than placebo treatment during the stable steroid phase (0.28 vs 0.54 [P = 0.006] and 14.6 % vs 23.3 % [P = 0.009], respectively) and during the steroid reduction phase (0.39 vs 0.66 [P = 0.003] and 21.3 % vs 32.3 % [P = 0.004], respectively). Beclomethasone dipropionate reduction was significantly greater with omalizumab treatment than with placebo (median 75 % vs 50 % [P < 0.001]), and beclomethasone dipropionate discontinuation was more likely with omalizumab (39.6 % vs 19.1 % [P < 0.001]). Improvements in asthma symptoms and pulmonary function occurred along with a reduction in rescue beta-agonist use. Omalizumab was well tolerated, with an adverse events profile similar to that of placebo.

In 1998 Frew (37) studied 19 allergic asthmatic subjects who received 9 week treatment with Omalizumab. The treatment reduced the serum IgE, increased the dose of allergen needed to provoke an early asthmatic response, reduced the mean maximal fall in FEV1 during the early and late responses.

In 1999 Fahy et al (38) tested wheter direct delivery of Omalizumab to the airway might have the same effect as intravenously, in a randomized, double-blind study in 33 subjects with mild allergic asthma. The airway responses to aerosolized allergen were determined at baseline, after 2 and 8 week of once daily treatment with aerosolized placebo (n = 11), aerosolized E25 1 mg (n = 12) or aerosolized E25 10 mg (n = 10), and after 4 week of treatment withdrawal. E25 was detectable in the serum during aerosol treatment, although serum IgE did not change significantly in any of the three groups. Both doses of E25 were not more effective than placebo in attenuating the early phase responses to allergen at both times during treatment. Altough aerosolized E25 was generally well tolerated, one subject receiving aerosolized E25 10 mg daily was found to have serum IgG and IgA antibodies to E25. They conclude that aerosol administration of Omalizumab does not inhibit the airway responses to inhaled allergen in allergic asmathic subjects. They especulated that the observed lack of efficacy may be due to the inabilityments surrounding IgE effector cells to neutralize IgE arising from local airway and pulmonary sources and IgE arising from the vascular space. The aerosol route of delivery of monoclonal antibodies may be more immunogenic than the parenteral route.

Allergic rhinitis

Adelroth et al (39) evaluated whether recombinant humanized (rhu)MAb-E25 could control symptoms and reduce intake of concomitant medication in seasonal allergic rhinitis (SAR) induced by birch pollen if given subcutaneously in a dose schedule predicted to reduce serum free IgE levels below 25 ng/mL. They studied 251 adult subjects with a history of SAR and a positive skin test response to birch pollen to receive 300 mg of rhuMAb-E25 or placebo given 2 or 3 times during the season, depending on baseline IgE levels. The primary efficacy variable was the subject's average daily nasal symptom severity score (sneezing, itching, runny, and stuffy nose) from diary data collected over the double-blind treatment period. Secondary efficacy variables included the average number of rescue antihistamine tablets per day, the proportion of days with any SAR medication use, and rhinoconjunctivitis-specific quality of life (RQLQ). Significant between-treatment differences in favor of rhuMAb-E25 were observed in average daily nasal symptom severity scores, the average number of tablets of rescue antihistamines per day, the proportion of days with any SAR medication use, and all domains of RQLQ. Serum-free IgE levels were markedly lower in rhumAb-E25-treated subjects and

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were associated with clinical effectiveness. Recombinant humanized mAb E25 was well tolerated. No anti-rhuMAb-E25 antibodies were detected.

Nayak et al (40) report that subcutaneous Omalizumab 150 or 300 mg given every 3 or 4 weeks was effective in the treatment of ragweed-induced seasonal alergic rhinitis. Omalizumab-treated patients had improvements in total RQLQ scores of 0.42 and 0.43 (150 mg and 300 mg, respectively) compared with placebo recipients after 12 weeks of treatment (p < 0.025).

Casale et al (41) saw that nasal and ocular symptom scores were significantly reduced in the group receiving Omalizumab (p < 0.012) and the average number of antihistamine tablets required per day was approximately half that needed by placebo recipients throughout the pollen season (< 0.20 vs 0.37, p < 0.012).

CONCLUSIONS

Omalizumab was also effective intravenous and subcutaneous, but not inhaled, in the treatment of adults and children with allergic asthma, demonstrating improvements in health-related quality-of-life and significant dosage reductions of inhaled corticosteroids and rescue medications. However, at present it is unclear wether this drug is effective in patients with polysensitization (i.e. patients suffering from mite, fungal and pollen allergy) or is effective in patients which have manifestations of their allergy in different organs (30).

Administration of omalizumab to patients with allergic asthma and rhinitis resulted in a rapid dose-dependent suppression of serum free IgE levels.

Compared with placebo, Omalizumab was safe and effective in controlling birch pollen-induced seasonal allergic rhinitis symptoms, with less concomitant medication use and improved quality of life.

Adverse events were infrequent in clinical trials of Omalizumab, and not significantly different from placebo. The most frequent drug-related event was mild to moderate urticaria, and it does not induce anaphylaxis, and the occurrence of antibodies against anti-IgE MAb is sporadic

Omalizumab, the recombinant humanized monoclonal antibody which specifically binds to the C epsilon3 domain of immunoglobulin (Ig) E, has potential as a treatment for subjects with moderate

or severe allergic asthma and seasonal allergic rhinitis.

RESUMEN

El papel causal de la inmunoglobulina E (IgE) en la activación de la cascada bioquímica que da lugar a la enfermedad alérgica está bien establecido. Los tratamientos que inhiben selectivamente la actividad de la IgE son una lógica aproximación al remodelado de la respuesta alérgica. El Omalizumab es un anticuerpo monoclonal recombinante humanizado que se une específicamente al dominio Cϵ3 de la inmunoglobulina E (IgE), el sitio de unión de alta afinidad del receptor de la IgE. Los pacientes con asma alérgica moderada o grave y rinitis estacional

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alérgica tratados con el anticuerpo anti-IgE (Omalizumab) presentaron un claro beneficio clínico, así como una reducción del uso de corticoides. La administración intravenosa o subcutánea de anti-IgE en pacientes atópicos reduce los niveles plasmáticos de IgE a cifras similares a las de individuos no atópicos. La terapia anti-IgE ofrece protección frente a la broncoconstricción inducida por alergenos y la reducción de las necesidades de beta 2-agonistas de corta duración y corticoides inhalados en pacientes asmáticos, así como una reducción de la intensidad de los síntomas en pacientes con rinitis alérgica. Los efectos adversos fueron poco frecuentes en los ensayos con Omalizumab, y no mostraron diferencias significativas con respecto al placebo. El más frecuente de ellos fue urticaria moderada a intensa. El tratamiento no provocó reacciones anafilácticas, y la presencia de anticuerpos frente a anti-IgE fue esporádica. Los resultados de los estudios sugieren que el tratamiento con anticuerpos monoclonales anti-IgE humanizados aportan un beneficio en el tratamiento de las enfermedades alérgicas.

Palabras clave: Omalizumab. RhuMAb-E25. Anti-IgE. Asma. Rinitis.

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