

# Treatment of asthma with anti-immunoglobulin E monoclonal antibody

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## ABSTRACT

*Clinical experience with anti-immunoglobulin E monoclonal antibody therapy (i.e., omalizumab) for asthma is maturing. Now several years after U.S. Food and Drug Administration approval and release, more studies of the clinical efficacy and safety of omalizumab have been published. We are gaining a better understanding of those patients with asthma who are likely to benefit from the therapy. The large majority of patients with asthma who meet the U.S. Food and Drug Administration–approved criteria for omalizumab therapy have severe persistent asthma. Additionally, in patients with severe disease, several predictive markers of clinical improvement with omalizumab therapy have been identified recently. There is good reason to have increasing comfort with omalizumab therapeutic trials, especially in those with severe asthma. (Allergy Asthma Proc 27:S24–S28, 2006)*

## IgE AND ATOPY IN ASTHMA

A compelling burden of evidence substantiates the pathogenic role of Immunoglobulin E (IgE) in asthma. IgE is a key bifunctional linker between the recognition of specific allergens and the activation of IgE receptor-bearing cells, leading to a cascade of immediate- and late-phase immune responses that characterize allergen-mediated asthma. Allergen sensitization occurs early in asthma development such that, in lower school-age children, 88% are already sensitized to at least one common aeroallergen.<sup>1</sup> Even in the preschool years when coughing or wheezing episodes with common respiratory viral infections are common, early sensitization to inhaled allergens is associated with persistent disease.<sup>2,3</sup> It is well established that the combination of IgE sensitization to indoor allergens with high levels of allergen in the home is associated with increased asthma severity. Although the most relevant allergen sensitization/exposure pairs may change depending on locale and household (e.g., dust mites, cats, dogs, and *Alternaria* in U.S. metropolitan areas and cockroaches and rats in inner cities),<sup>1,4,5</sup> the theme remains the same. The importance of this sensitization/exposure combination in asthma severity is substantiated further when asthma improves after the offending allergen(s) is completely eliminated or greatly reduced in homes.<sup>6–8</sup>

## EFFICACY OF ANTI-IgE THERAPY IN CLINICAL TRIALS

Given the importance of allergen-mediated reactions and inflammation in asthma, together with the limitations in effectively reducing problematic allergens to low enough levels to improve matters significantly, interventions to abrogate the allergic immune response in the susceptible asthmatic patients seem rational. The biological basis for the development of anti-IgE humanized monoclonal antibody therapy and the postulated mechanisms of action of omalizumab are described in other articles of this supplement (i.e., Chang<sup>9</sup>; Soresi and Togias<sup>10</sup>). Clinical trials performed thus far have not only established the effectiveness of omalizumab in the treatment of asthma in adults, but also in adolescents and children with difficult-to-control asthma. These clinical trials have provided the basis for the U.S. Food and Drug Administration (FDA) approval and the current status of omalizumab now available for the treatment of patients with inadequately controlled asthma, aged  $\geq 12$  years old, with perennial allergen sensitization.

## Adult and Adolescent Patients

In a U.S. FDA phase III, double-blind, placebo-controlled trial, 525 patients (12–75 years old) with severe allergic asthma on daily inhaled corticosteroids (ICS) received omalizumab ( $\geq 0.016$  mg/kg per IgE [IU/mL]) or placebo subcutaneously every 2–4 weeks.<sup>11</sup> To minimize possible confounding effects of other treatment regimens on study results, ICS doses were maintained for the initial 16 weeks and then tapered over the next 12 weeks. Compared with placebo, patients who received omalizumab experienced fewer exacerbations during both the ICS-maintenance and the ICS-tapering phases, and their exacerbations were of shorter duration. Omalizumab treatment also was associated with

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greater reduction in ICS usage and more ICS discontinuation. This study was extended for an additional 24 weeks and included a total of 460 patients who were instructed to record symptoms daily.<sup>12</sup> The results of this study revealed that continued therapy with omalizumab is efficacious and well tolerated. Significantly fewer exacerbations per patient occurred in those continuing on omalizumab versus placebo (0.60 versus 0.83, respectively;  $p = 0.023$ ); there also was significantly lower ICS dosages compared with placebo (mean beclomethasone dipropionate [BDP] equivalent dose, 227 versus 335  $\mu\text{g}/\text{day}$ ;  $p < 0.001$ ). Extended use of omalizumab was well tolerated, with comparable side effects in the omalizumab and placebo arms.

Another phase III trial of similar design included 546 patients 12–76 years old with moderate-to-severe allergic asthma and revealed comparable beneficial results.<sup>13</sup> Participants who received omalizumab experienced significantly fewer exacerbations, and reduction in daily ICS dose from the starting dose also was greater in the omalizumab versus placebo groups (83.0% versus 50.0%;  $p < 0.001$ ). In addition, specific parameters such as peak expiratory flow and forced expiratory volume in 1 second ( $\text{FEV}_1$ ) were significantly improved in patients receiving omalizumab compared with placebo. The overall incidence of adverse effects was comparable between treatment arms.

A recent study assessed the ability of omalizumab ( $\geq 0.016$  mg/kg per IgE [IU/mL] per 4 weeks) to improve disease control and reduce ICS in patients with severe allergic asthma who were receiving high-dose ICS.<sup>14</sup> A total of 246 patients 12–75 years old entered this randomized, double-blind, placebo-controlled study for a period of 32 weeks after a 6- to 10-week run-in phase. Omalizumab therapy improved asthma symptoms, rescue medication use, asthma-related quality of life, and  $\text{FEV}_1$  at all time points of the study. Median reductions in ICS dose were significantly greater in the omalizumab versus placebo groups (60% versus 50%, respectively;  $p = 0.003$ ). Collectively, the results of these studies show that for patients with severe asthma, omalizumab can improve asthma control with less ICS requirements.

### Pediatric Study

In a phase III trial of similar design to the phase III trials conducted in adult and adolescent patients, pediatric patients who received omalizumab also experienced improvements in their asthma.<sup>15</sup> In this study, a total of 334 children 6–12 years old with moderate-to-severe allergic asthma were randomized to receive either omalizumab ( $\geq 0.016$  mg/kg per IgE [IU/mL] per 4 weeks) or placebo in addition to ICS. A significantly greater proportion of omalizumab-treated children were able to decrease their ICS dose than placebo-

treated children ( $p = 0.002$ ), and the median reduction in BDP dose at 4 weeks from baseline values was greater in the omalizumab group (100% versus 67%, respectively;  $p = 0.001$ ). Moreover, BDP doses could be discontinued completely in 55% of the omalizumab-treated patients compared with 39% of patients who received placebo ( $p = 0.004$ ), and omalizumab-treated participants experienced fewer asthma exacerbations and required less unscheduled physician visits (omalizumab versus placebo, 12.9% versus 30.3%;  $p = 0.001$ ). This study was extended for an additional 24 weeks<sup>16</sup> in a total of 225 patients who received uninterrupted dosing of omalizumab. From the start of the double-blind study through the extension period, the mean reduction in ICS dose achieved during the original study was generally maintained during the extension. The incidence of adverse events in patients treated with omalizumab for 52 weeks generally was comparable with placebo. Although omalizumab is currently not U.S. FDA approved for use in children with asthma who are  $<12$  years of age, these studies provide evidence of the efficacy of omalizumab therapy in these younger-age children.

### Safety of Anti-IgE Therapy in Clinical Trials

Safety data from 12 FDA phase IIB/III clinical trials of omalizumab therapy of patients with IgE-mediated asthma and other allergic diseases have been reviewed recently.<sup>17</sup> The pooled data analysis revealed that the frequency of adverse events was similar in the omalizumab-treated and control groups, and no organ-specific toxicity was found. Anaphylactic reactions were very rare and there was no significant difference in the occurrence of anaphylactic episodes between controls (0.05%, 1 of 2019 patients) and omalizumab-treated patients (0.09%, 3 of 3224 patients). The incidence of other hypersensitivity reactions, including injection site reactions, urticaria, dermatitis, and pruritus, were similar in the omalizumab and control groups.

In the U.S. FDA phases I-III clinical studies, malignancies were observed in 0.48% of omalizumab-treated patients versus 0.22% of placebo-treated patients, which was numerically higher but not statistically significant. The observed malignancies in the omalizumab-treated patients were of a wide variety (e.g., breast, skin, prostate, and parotid gland). A team of expert oncologists reviewed each case and concluded that there was no evidence of causal association between omalizumab and tumors and that the malignancies most likely existed before treatment.<sup>17</sup>

### BASELINE PREDICTORS OF RESPONSE TO OMALIZUMAB

Because these numerous clinical trials have assessed the efficacy of omalizumab for persons with severe

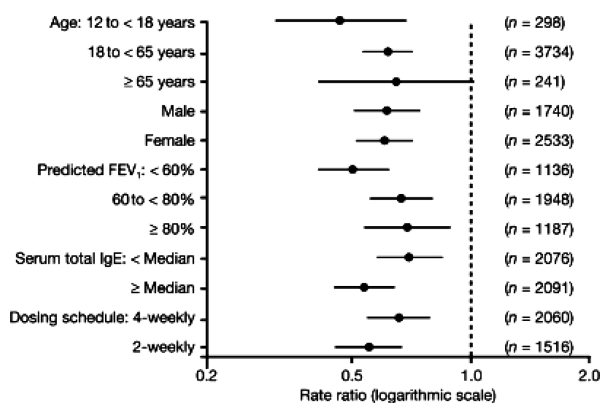


**Figure 1.** Relative rates of asthma exacerbations across subgroups in seven pooled studies. Point estimates and 95% confidence intervals for asthma exacerbation rate ratio (omalizumab/control) are plotted. Source Ref. 18.

asthma to varying extents in individual studies, some helpful efforts to pool the experience in these clinical trials have been made to glean additional insights for severe asthma and response predictors. Analysis of pooled data from seven clinical studies that included 4308 randomized study participants (2511 receiving omalizumab versus 1797 placebo controls) revealed that 93% of these study participants met the criteria for severe persistent asthma as defined in the 2002 Global Initiatives for Asthma guidelines.<sup>18</sup> Compared with placebo, omalizumab significantly reduced the rate of asthma exacerbations by 38% ( $p < 0.0001$ ). Correspondingly, omalizumab reduced unscheduled doctor visits by 47% ( $p = 0.0003$ ), emergency room visits by 61% ( $p = 0.01$ ), and hospital admissions by 52% ( $p = 0.04$ ). A number of baseline factors were evaluated also for their possible associations with asthma exacerbations. The pooled data were evaluated in subgroups

arranged by age, gender, baseline FEV<sub>1</sub> (% predicted), baseline total serum IgE, and 4-weekly versus 2-weekly dosing schedules (Fig. 1). In essentially all subgroups, although omalizumab therapy was associated with an overall lower rate of asthma exacerbations, there was a tendency toward lower rates of asthma exacerbations in participants with FEV<sub>1</sub> values <60% predicted and in the younger participants (*i.e.*, <18 years of age).

Response predictors were further evaluated in a pooled analysis of two large, multicenter studies, which, when combined, included 1070 participants (542 treated with omalizumab versus 528 with placebo).<sup>19</sup> The criterion measure of response to treatment was a composite definition of response based on no asthma exacerbations during the study period together with one of the following additional measures of improvement: (1) reduced asthma symptoms, (2) reduced rescue medication usage, (3) improved lung function, and/or (4) improved asthma-related quality of life. Of those who showed an improved response to treatment by the end of the 16-week study period, onset of improvement was observed in 61% during the first 4 weeks, which increased to 87% by 12 weeks. Although many baseline characteristics were considered as potential response predictors, the following three emerged as the most significant: (1) high ICS dose (BDP,  $\geq 800 \mu\text{g/day}$ ), (2) history of emergency asthma treatment in the past year, and (3) FEV<sub>1</sub>  $\leq 65\%$  predicted (Fig. 2). Of the study population, the 76% with at least one of these three positive predictors were significantly more likely to improve with omalizumab treatment (odds ratio, 2.25; 95% confidence intervals, 1.68–3.01). Although participants with two or three positive predictors were significantly more likely to improve with omalizumab; participants with all three indicators

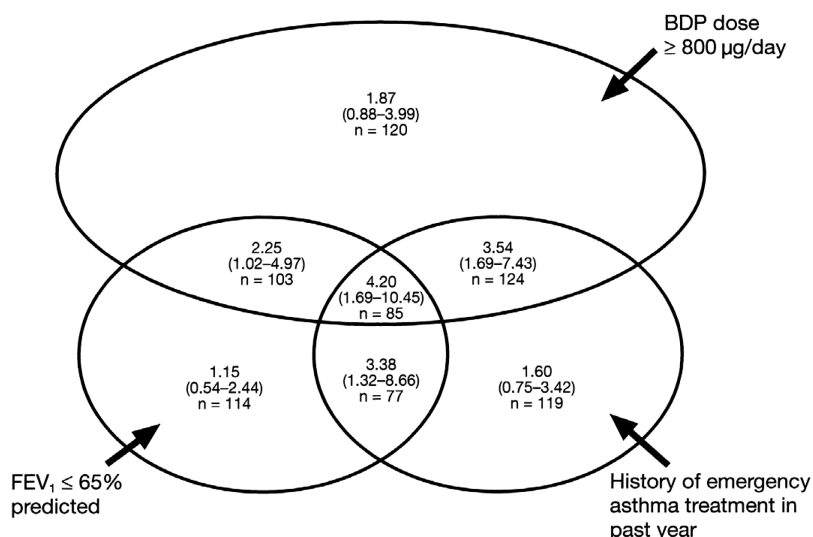


**Figure 2.** Venn diagram of odds ratios and 95% confidence intervals for improvement with omalizumab therapy versus placebo, based on a composite definition of response, according to three high-severity indicators. BDP, beclomethasone dipropionate. Source Ref. 19.

Table 1 U.S. FDA Criteria and Predictors of Improvement with Omalizumab Therapy

| U.S. FDA-Approved Indications                                                                                     | Response Predictors <sup>19</sup>                              |
|-------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| Age $\geq 12$ years                                                                                               | FEV <sub>1</sub> $\leq 65\%$ predicted                         |
| Asthma, moderate to severe                                                                                        | Emergency room visits in the past year                         |
| Inadequately controlled by ICS therapy                                                                            | ICS dose, BDP $> 800$ $\mu\text{g}/\text{day}$ (or equivalent) |
| Sensitization to at least one perennial aeroallergen<br>( <i>e.g.</i> , mites, cockroaches, cats, dogs, and mold) |                                                                |

had the greatest likelihood of improvement with omalizumab (odds ratio, 4.20; 95% confidence intervals, 1.69–10.45).

## CONCLUSIONS

Omalizumab has a well-established record in clinical research of improving asthma control and reducing asthma severity, exacerbations, and medication usage. The FDA-approved criteria appear to be good indicators for patients with asthma who are likely to improve with omalizumab therapy (Table 1). In addition, the use of multiple indicators of more severe disease also increase the likelihood of subsequent improvement in asthma with omalizumab therapy; these predictors include FEV<sub>1</sub>  $\leq 65\%$  predicted, emergency room visit(s) in the past year, and/or high-dose ICS controller therapy (Table 1). These criteria should justify a trial of omalizumab therapy in people with asthma who meet them.

For example, poor responders to ICS therapy are likely to have poorly controlled asthma, more exacerbations, and be placed on escalating doses of ICS in an attempt to gain a dose-response effect from this treatment. However, benefit from ICS therapy may taper or plateau at higher doses.<sup>20</sup> The recognition that allergic immune responses also may contribute to an acquired, reversible form of corticosteroid insensitivity<sup>21,22</sup> has led to an alternative therapeutic anti-IgE regimen, which, by blocking allergic immune responses, may reverse corticosteroid insensitivity and allow ICS to be more effective. It also is intriguing to consider the tendency of younger children versus adults treated with omalizumab to experience better outcomes (*e.g.*, greater reductions in asthma exacerbations).<sup>15</sup> Although currently there is less known about the efficacy and safety of omalizumab in children, especially those  $< 12$  years of age, some well-conducted studies have been performed in children ages 6–12 years old, with promising findings.<sup>15,16</sup> Other indicators have been studied that appear to have less predictive value of omalizumab efficacy, such as lack of effects of either baseline total serum IgE levels or gender. Collectively, these studies are not only providing response indicators suggesting the safety of omalizumab therapy on a short-term basis, but also, as postrelease experience

continues to increase over the years with greater drug usage in the treatment of sufficiently large numbers of asthmatic patients, valuable information will be generated concerning long-term safety issues, which will be of interest to both health care providers and the patients whom we serve.

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