

# PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the  
University of Virginia Children's Hospital

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Volume 13 Number 6

June 2007

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## Omalizumab for the Management of Refractory Allergic Asthma in Children

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Omalizumab, a recombinant humanized monoclonal antibody to IgE, was approved by the Food and Drug Administration (FDA) on June 20, 2003.<sup>1</sup> It is currently indicated for the management of moderate to severe allergic asthma refractory to standard therapies in adults and adolescents 12 years of age and older.<sup>2</sup> While not yet approved by the FDA for pediatric use, omalizumab has been studied in children with asthma, as well as in patients with atopic dermatitis and chronic urticaria. This issue of *Pediatric Pharmacotherapy* will review the pharmacology of omalizumab and describe the major studies supporting its use.

### Mechanism of Action

Omalizumab forms complexes with IgE, inhibiting its binding to high-affinity  $F_{c\epsilon}$  receptors ( $F_{c\epsilon}RI$ ) on the surface of mast cells and basophils. This produces a dose-dependent decrease in serum unbound IgE levels, as well as a decrease in the number of  $F_{c\epsilon}$  receptors expressed on several cell types, including circulating basophils. As a result, the amount of inflammatory mediators released by these cells is lessened, reducing patient symptoms. In clinical trials, omalizumab decreased both early and late-phase allergic reactions, improved pulmonary function, as measured by forced expiratory volume in one second ( $FEV_1$ ), and increased the amount of allergen required to produce bronchoconstriction.<sup>1-4</sup>

### Clinical Experience

A number of clinical trials have been conducted to demonstrate the efficacy and safety of omalizumab in adolescents and adults, including seven large-scale randomized, placebo-controlled studies.<sup>5</sup> The most recent of these is the Investigation of Omalizumab in Severe Asthma Treatment (INNOVATE) trial.<sup>6</sup> A total of 419 patients between the ages of 12 and 75 years were included in this 28-week international randomized, double-blind, placebo-controlled study. Patients were eligible for enrollment if their asthma symptoms were not controlled on

high-dose inhaled corticosteroids and long-acting beta<sub>2</sub>-adrenergic agonists. The primary outcome variable, rate of clinically significant asthma exacerbations, was significantly lower in the omalizumab group (0.68 versus 0.91 in the controls,  $p=0.042$ ). Severe exacerbations, defined as a peak expiratory flow or  $FEV_1 < 60\%$  of personal best, were also reduced (0.24 versus 0.48,  $p=0.002$ ), as well as the rate of emergency room visits (0.24 versus 0.43,  $p=0.038$ ). In addition, more patients in the omalizumab group had improvement in their scores on the Juniper Asthma Quality of Life Questionnaire (60.8% versus 47.8% of controls,  $p=0.008$ ).

The treatment group in the INNOVATE trial also had significant improvement in morning peak expiratory flows ( $p=0.042$ ),  $FEV_1$  percent predicted values ( $p=0.043$ ), and total asthma symptom scores ( $p=0.039$ ). Sixty-four percent of the patients enrolled in the study rated the effectiveness of omalizumab as excellent or good. The incidence of adverse effects was similar between the groups. As with previous studies, the authors concluded that omalizumab was a useful addition to the management of patients with inadequately controlled severe asthma.

The first pediatric trial of omalizumab was conducted by Milgrom and colleagues in 2001. The authors enrolled 334 children between 6 and 12 years of age with moderate to severe allergic asthma in a 28-week randomized, double-blind, placebo-controlled study.<sup>7</sup> All of the children were being treated with inhaled beclomethasone and required intermittent bronchodilator therapy. The trial consisted of a 4 to 6-week run-in phase, followed by a 16-week treatment phase without adjustment of concomitant therapy, followed by a 12-week steroid dose-reduction phase. Patients were randomized to receive either omalizumab or placebo every 2 or 4 weeks. As in the adult trials, dosing was based on weight and serum IgE levels, with an approximate dose of 0.016 mg/kg/IgE (IU/mL) per 4 weeks. In the last phase of the trial, the inhaled steroid dose was

reduced 25% every 2 weeks for 8 weeks. Patients were then maintained on the lowest effective dose. Those who developed worsening symptoms were returned to their previous steroid dose.

Serum IgE levels were reduced by 95% to 99% in the omalizumab group. There was a significant reduction in steroid dose between the omalizumab-treated patients and the controls ( $p=0.001$ ). Fifty-five percent of the omalizumab patients had their beclomethasone withdrawn completely, compared to 39% of the controls ( $p=0.004$ ). There was no significant difference in the number of asthma exacerbations between the groups, but the severity of the exacerbations was less in the children receiving omalizumab. There were more clinic visits in the controls (30.3% versus 12.9% in the treated patients), and more placebo-treated children had a decrease in their peak flows (17.4% versus 6.7%) or a need for increased rescue medication use (21.1% versus 11.6%, all  $p$  values  $<0.002$ ).

Quality of life assessments were also conducted during the trial using the Pediatric Asthma Quality of Life Questionnaire (PAQLQ).<sup>8</sup> This scale ranges from a score of 1 for significant impairment to 7 for no impairment. At baseline, the mean PAQLQ scores were 5.5 for the omalizumab group and 5.4 for the controls. At the end of the 28-week study, the children receiving omalizumab reported greater improvement in their PAQLQ scores compared to the controls. In addition, the authors reported that children in the omalizumab group had fewer missed school days (0.65 days compared to 1.21 days for the controls,  $p=0.04$ ).

#### Pharmacokinetics

Omalizumab is administered by subcutaneous injection. It has an average bioavailability of 62%. It is slowly absorbed after injection, with peak serum concentrations occurring 7 to 8 days after administration. Omalizumab is not taken up into organs or tissues. It has an apparent volume of distribution of approximately 0.08 L/kg. The trimeric and hexameric omalizumab-IgE complexes are cleared from the body by degradation in the hepatic reticuloendothelial system and endothelial cells. Omalizumab has an approximate serum elimination half-life of 26 days, with a clearance rate of  $2.4 \pm 1.1$  mL/kg/day. Increasing body weight results in a more rapid clearance.<sup>1,2</sup>

#### Drug Interactions

There are currently no known drug interactions with omalizumab, but no formal drug interaction studies have been conducted.<sup>1,2</sup>

#### Adverse Effects

On February 21, 2007, the FDA issued an alert to prescribers regarding new reports of severe allergic reactions, including anaphylaxis, following omalizumab administration.<sup>9</sup> Rare severe hypersensitivity reactions had been observed during premarketing clinical trials, including three patients who developed anaphylaxis, but all of these cases occurred within 2 hours after drug injection. The new reports include patients whose symptoms occurred up to 24 hours or more after administration of omalizumab. As a result of these new reports, a black box warning has been added to the prescribing information highlighting the need for health care professionals who administer the drug to be prepared to manage severe hypersensitivity reactions and the need to educate patients about the signs and symptoms of anaphylaxis.

The manufacturer has reported 20 cases of malignancy in 4,127 patients treated with omalizumab during clinical trials, including breast, skin (non-melanoma and melanoma), prostate, parotid, thyroid, bladder, pancreas, and rectal cancers. One case of non-Hodgkin's lymphoma was also reported. The rate of malignancy in patients receiving omalizumab (0.5%) was slightly higher than that of the controls in those trials (five cases in 2,236 controls or 0.2%). At this time, no causal association between omalizumab use and cancer has been established, but continued surveillance is needed.<sup>1,2,4</sup>

Omalizumab has been well tolerated by most patients. In premarketing clinical trials, the most commonly reported adverse effects were injection site reactions (reported in 45% of patients), viral infections (23%), upper respiratory tract infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%). Other adverse reactions reported included arthralgia (8%), pain (2-7%), fatigue (3%), dizziness (3%), and pruritus, dermatitis, or earache (2%). All of these reactions were reported in similar rates in the control patients, except for severe injection site reactions (12% in the omalizumab group compared to 9% in controls). The frequency of adverse reactions did not appear to vary among age groups.<sup>1,2</sup>

Similar results have been reported in post-marketing pediatric trials. Berger and colleagues combined the results of their 28-week study described previously and a 24-week open-label extension study to evaluate the long-term safety of omalizumab in children.<sup>10</sup> A total of 202 children between 6 and 12 years of age were

included in the 52-week study. The most commonly reported adverse effects included upper respiratory tract infection (in 47% of children), headache (43%), pharyngitis (35%), and urticaria (5%). One patient discontinued therapy after developing hives after the 7<sup>th</sup> and 8<sup>th</sup> injections. There were no differences between the rates of these adverse effects in the treated patients and the children who received placebo during the 28-week comparison study.

#### Dosing Recommendations

Omaliuzumab must be administered by a health care provider in a setting equipped to manage severe hypersensitivity reactions. The recommended dose of omaliuzumab ranges from 150 to 375 mg and is administered every 2 or 4 weeks. The dose and dosing interval are determined by patient weight and pretreatment serum IgE levels. In patients weighing 30 to 60 kg, the following guidelines may be used:

| <b>Baseline IgE (IU/mL)</b> | <b>Dose</b>          |
|-----------------------------|----------------------|
| < 100                       | 150 mg every 4 weeks |
| 100-300                     | 300 mg every 4 weeks |
| 300-400                     | 225 mg every 2 weeks |
| 400-600                     | 300 mg every 2 weeks |
| 600-700                     | 375 mg every 2 weeks |

Dosing recommendations for larger weight groups are available in the prescribing information on the manufacturer's website at [www.xolair.com](http://www.xolair.com).<sup>1-4</sup>

Repeat IgE levels are not necessary, and no further dose adjustment is needed. Dosage adjustment is not necessary for patients with hepatic or renal dysfunction, but may be needed for patients with a significant weight change during treatment. Doses more than 150 mg should be divided and administered at two injection sites.<sup>1-4</sup>

#### Availability

Omaliuzumab (Xolair<sup>®</sup>; Genentech) is available in 75 mg and 150 mg single-use vials. The vials do not contain preservatives. The drug must be reconstituted with sterile water prior to administration. Once reconstituted, the solution should be used within 8 hours if refrigerated or within 4 hours if stored at room temperature. Omaliuzumab is available only through specialty pharmacies designated by the manufacturer. It is currently available through Caremark Rx, Inc., CuraScript Pharmacy, Inc., Accredo Nova Factor, Inc., and Option Care, Inc. Prescribers may make arrangements for the drug to be delivered to their practice site or to the patient's home.<sup>1,2</sup>

#### Place in Therapy

The high cost of omaliuzumab, approximately \$500 to \$3,000 per month, in addition to the need for monthly or twice monthly clinic visits, must be balanced with the potential savings in reduced hospitalizations and emergency medical treatment. Several investigators have attempted to determine which patients would be most likely to benefit from this therapy. After evaluating the results of the preliminary clinical trials conducted in adults, Bousquet and colleagues suggested that the patients who would derive the greatest benefit from therapy would be those with poor underlying pulmonary function (an FEV<sub>1</sub> < 60%), those routinely utilizing emergency care, and those requiring high doses of inhaled corticosteroids.<sup>11</sup> The American College of Chest Physicians recently published a practice management guideline to help clinicians determine the proper role for omaliuzumab therapy.<sup>12</sup> Based on the currently available literature, the authors of the guideline suggested that omaliuzumab be considered only as a second-line therapy in patients with refractory asthma, after all attempts have been made to optimize use of traditional therapies.

The role of omaliuzumab in the treatment of children with allergic asthma is not yet clearly defined. In their 2005 review, Briars and Diaz suggested that omaliuzumab be considered in children requiring high doses of inhaled corticosteroids or systemic steroids.<sup>13</sup> The authors suggested that these patients are at greater risk for the adverse effects associated with steroid use, including growth suppression, lability in mood, and hypertension; and therefore, may have the greatest benefit from an alternative therapy. They cite the high rate of beclomethasone discontinuation (55%) in the study conducted by Milgrom and colleagues,<sup>7</sup> which persisted in the one-year open-label continuation study,<sup>10</sup> as evidence of the positive impact of omaliuzumab on long-term asthma management.

#### Summary

Omaliuzumab offers a unique mechanism for the treatment of allergic asthma in patients who remain symptomatic despite optimal use of inhaled corticosteroids, beta-agonists, and leukotriene modifiers. While it is generally well tolerated, administration of omaliuzumab has resulted in severe anaphylactic reactions as long as 24 hours after injection. In addition to the potential for significant adverse effects, the cost of omaliuzumab therapy must be considered when determining the appropriate place of this therapy in the management of children with refractory asthma.

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## Pharmacology Literature Review

### Prolactin Release with Risperidone

Elevation in serum prolactin levels is a known adverse effect of the atypical antipsychotics, including risperidone. It may be more pronounced in patients with a phenotypic rapid metabolism of the drug via cytochrome P450 2D6 enzymes (CYP2D6). In this study, prolactin levels were obtained in 25 children (5 to 15 years of age) with pervasive developmental disorders who were receiving risperidone. The average dose used in the patients was 0.06±0.03 mg/kg/day. Levels were obtained at baseline and after 8 and 24 weeks of treatment. Mean prolactin levels increased from 7.8±8.0 ng/mL at baseline to 33.2±12.8 ng/mL at week 8, with a decrease to 28.8±13.6 ng/mL at week 24. There were positive correlations between the prolactin concentration and the weight-adjusted dose, the number of functional CYP2D6 genes, and the serum 9-hydroxyrisperidone concentration. In this patient sample, the increase in prolactin levels was not associated with any clinical

adverse effects. Troost PW, Lahuis BE, Hermans MH, et al. Prolactin release in children treated with risperidone: impact and role of CYP2D6 metabolism. *J Clin Psychopharmacol* 2007;27:52-7.

### Valproic Acid Infusions

The authors of this paper present a retrospective review of 26 children (ages 1-16 years) who received continuous infusions of valproic acid to provide rapid achievement of therapeutic serum concentrations. Approximately 2/3 of the patients were being treated for seizures, while the remaining patients were being treated for migraines. Patients were given a mean loading dose of 28.5±5.2 mg/kg IV, followed by an infusion of 1±0.2 mg/kg/hr. The mean serum concentration following the load was 83.3±22.8 mcg/mL, with a mean concentration at steady-state of 80.0±26.0 mcg/mL. At steady-state, 92% of the children had levels within the desired range of 50-125 mcg/mL. Eighty-five percent of the patients demonstrated a partial or complete response to therapy. Based on their results, the authors suggest that this method may be useful to provide rapid achievement of target serum concentration. Taylor LM, Farzam F, Cook AM, et al. Clinical utility of a continuous intravenous infusion of valproic acid in pediatric patients. *Pharmacotherapy* 2007;27:519-25.

### Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 5/25/07:

1. Hydroxocobalamin (Cyanokit®) was added to the Formulary for the management of cyanide poisoning, with restriction to Toxicology.
2. Prussian Blue (Radiogardase®) was added to the Formulary for the treatment of patients with internal contamination with thallium or radioactive cesium, with restriction to Toxicology.
3. The restriction on the use of decitabine was removed.
4. A request for addition of lapatinib (Tykerb®) to the Outpatient Formulary was rejected.

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