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## Case report

# Improvement of asthma control with omalizumab in 2 obese pediatric asthma patients

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**Background:** Dosing of the anti-IgE antibody (omalizumab) in the treatment of allergic asthma depends on serum IgE concentration and body weight. It is unclear whether omalizumab is therapeutically effective in obese patients with difficult-to-control asthma whose body weights fall outside dosing guidelines.

**Objective:** To report the efficacy of omalizumab in 2 obese pediatric patients with severe persistent asthma whose high body weights placed them outside current dosing guidelines.

**Methods:** Omalizumab was given at maximum doses to both patients. Standard asthma therapy was continued throughout the treatment period. Multiple parameters of asthma disease activity were followed at every health encounter for approximately 1 year during and before omalizumab treatment. These parameters included asthma disease severity and activity, pulmonary functions, daily inhaled corticosteroid requirements, systemic steroid rescue, and urgent care and emergency department visits and hospitalizations.

**Results:** While receiving omalizumab, both patients had improvements in asthma disease activity and reduction in systemic steroid requirements. One patient required fewer daily inhaled corticosteroids and achieved total asthma control.

**Conclusion:** Patients with difficult-to-treat asthma may benefit from receiving omalizumab even if they fall outside current dosing guidelines because of high body weight.

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## INTRODUCTION

The monoclonal antibody omalizumab, which is directed against IgE, is effective for the treatment of allergic asthma. Controlled and real-world studies have demonstrated that omalizumab therapy in patients with moderate to severe persistent asthma resulted in up to a 50% reduction in asthma exacerbations, including reduced hospitalizations, emergency department and urgent care visits, and rescue doses of systemic steroids. Diminished inhaled corticosteroid (ICS) requirements, improvements in quality of life, and pulmonary function test results have also been reported in most studies.<sup>1–6</sup> Similar clinical improvements have been demonstrated in asthmatic patients in whom asthma control has not been achieved with normal standard care.<sup>7,8</sup> Attenuation of airway inflammation manifested by a decrease in exhaled nitric oxide, bronchial eosinophils, and inflammatory cytokine staining has been shown in patients receiving omalizumab.<sup>2,3,9</sup> These studies validate a role for omalizumab therapy in asthma patients with unmet needs not relieved with normal standard care.

Omalizumab is currently only recommended by its manufacturer (Genentech, South San Francisco, CA) for patients

who have a certain combination of body weight and total serum IgE concentration. Patients who have excessive body weight are not eligible to receive omalizumab under present guidelines. Since there have been parallel increases in obesity and asthma during the last few decades, it is likely that a significant number of asthmatic patients are obese, and although a causal relationship between asthma and obesity has not been established, strong evidence suggests an association between the 2 disease states.<sup>10–14</sup> It is logical that significant numbers of these obese asthmatic patients have difficult-to-treat disease. Under current dosing guidelines, obese asthmatic patients are not eligible to receive a novel therapeutic agent that could result in asthma control unachievable with normal standard care.

In this case study, we describe 2 pediatric patients with severe persistent asthma whose high body weights precluded them from receiving omalizumab under current guidelines. Both patients had inadequate asthma control despite high-dose ICSs and required multiple courses of rescue systemic steroids yearly. Because of high disease burden, omalizumab was initiated at the maximum dose (375 mg every 2 weeks). We report improvements in asthma disease parameters after more than 1 year of treatment with omalizumab, including ICS requirements, asthma disease activity, and systemic steroids rescue. Further, we demonstrate real-time improvements in asthma disease activity during this period in these 2 patients.

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Table 1. Patient Characteristics

| Characteristics      | Patient 1                  | Patient 2                  |
|----------------------|----------------------------|----------------------------|
| Weight, lb           | 113                        | 120                        |
| Age, y               | 14                         | 13                         |
| IgE, IU/mL           | 459                        | 677                        |
| Asthma severity      | Severe persistent          | Severe persistent          |
| Most severe symptoms | Daily and nightly wheezing | Daily and nightly wheezing |
| FEV <sub>1</sub>     | <80%*                      | ≤80%*                      |
| Comorbid conditions  | AR, GERD, obesity          | AR, obesity                |
| Omalizumab dose      | 375 mg every 2 wk          | 375 mg every 2 wk          |

Abbreviations: AR, allergic rhinitis; FEV<sub>1</sub>, forced expiratory volume in 1 second; GERD, gastroesophageal reflux disease.

\* Both patients had an FEV<sub>1</sub> of greater than 12% reversibility after  $\beta_2$ -agonist use.

## CASE REPORTS

We describe 2 male patients, ages 13 and 14 years, with severe persistent asthma who had been treated by the Mobile Asthma Unit program (Breathmobile) of the Division of Allergy-Immunology, Los Angeles County+University of Southern California (LAC+USC) Medical Center. Initial asthma severity was classified as severe persistent in both patients because of daily and nightly asthma symptoms. Both patients required bronchodilator rescue medication at least 2 to 3 times daily. On initial spirometry, both patients had a forced expiratory volume in 1 second (FEV<sub>1</sub>) below 80% predicted with a postbronchodilator response of more than 12%, and both achieved an FEV<sub>1</sub> above 80% predicted after a 2.5-mg albuterol challenge. Both patients had coexisting allergic rhinitis, and 1 patient had clinical evidence of gastroesophageal reflux disease (Table 1). Percutaneous skin prick test results were positive in both patients for a range of seasonal and perennial aeroallergens, but neither patient had any positive reaction to food antigens. Allergic bronchopulmonary aspergillosis was excluded on the basis of negative precipitins antibodies to aspergillosis species, lack of eosinophilia, relatively low total IgE level (459 and 677 IU/L for patients 1 and 2, respectively), and normal chest CT scan with no bronchiectasis.

High-dose ICS therapy (1,880  $\mu$ g/d of fluticasone dipropionate) in combination with a long-acting bronchodilator (LABA) (salmeterol) and leukotriene receptor antagonist (LTRA) (montelukast) was initiated in both patients. Sys-

temic steroids were given in both patients until asthma symptoms were consistent with at least moderate persistent severity. Intranasal steroids (mometasone) and antihistamines (fexofenadine) were prescribed in both patients, and a proton pump inhibitor (omeprazole) was used with patient 1. Within 8 weeks of therapy, both patients had asthma disease activity consistent with moderate persistent severity and systemic steroid therapy was discontinued. The FEV<sub>1</sub> improved to above 80% predicted in patient 1 but remained below 80% predicted in patient 2. Despite high-dose ICS, LABA, and LTRA treatment, institution of allergen avoidance strategies, and treatment of allergic rhinitis and gastroesophageal reflux disease, both patients' asthma disease activity never improved beyond moderate persistent severity. Patient 2 continued to have an FEV<sub>1</sub> persistently below 80% predicted, whereas the lung function of patient 1 remained within normal limits. Both patients required oral steroid bursts approximately 2 to 3 times a year because of asthma exacerbations (Table 2). Repeated attempts to reduce ICS dose resulted in deterioration of asthma symptoms.

Both patients began omalizumab therapy, because despite normal standard care they were unable to improve asthma disease activity, wean daily ICS use, reduce rescue systemic steroid bursts, and improve lung functions (patient 2). Because of high disease burden, attending staff (K.Y.C.K. and C.A.J.) believed it was ethically obligatory to try omalizumab despite both patients being ineligible according to commercial dosing guidelines due to their body weights (Fig 1). Both

Table 2. Asthma Control During the Year Before Omalizumab Therapy While Receiving Standard Care\*

| Variable                                            | Patient 1                                                        | Patient 2                                                                               |
|-----------------------------------------------------|------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| Mildest asthma severity achieved (asthma activity)† | Moderate                                                         | Moderate                                                                                |
| Improved PFT results                                | Yes                                                              | No                                                                                      |
| ICS dose reduction                                  | No                                                               | No                                                                                      |
| Reduced systemic steroid rescue                     | No                                                               | No                                                                                      |
| Reason omalizumab treatment begun                   | Unable to improve severity or wean ICS, persistent exacerbations | Unable to improve severity or wean ICSs, persistent exacerbations, low FEV <sub>1</sub> |

Abbreviations: FEV<sub>1</sub>, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; PFT, pulmonary function test.

\* Patients were treated with high-dose ICSs (1,880  $\mu$ g/d of fluticasone), long-acting bronchodilators, and leukotriene receptor antagonists.

† This is the mildest asthma severity achieved for more than 50% of visits.

Every 2 week dosing

| Pretreatment<br>Serum IgE (IU/ml) | Body weight (Kg) |        |        |                    |
|-----------------------------------|------------------|--------|--------|--------------------|
|                                   | 30-60            | >60-70 | >70-90 | >90-150            |
| ≥30-100                           |                  |        |        |                    |
| >100-200                          |                  |        |        | 225mg              |
| >200-300                          |                  | 225mg  | 225mg  | 300mg              |
| >300-400                          | 225mg            | 225mg  | 300mg  |                    |
| >400-500                          | 300mg            | 300mg  | 375mg  | <i>Patient 1</i> ← |
| >500-600                          | 300mg            | 375mg  |        |                    |
| >600-700                          | 375mg            |        |        | <i>Patient 2</i> ← |

Dosing table adapted from omalizumab package insert

Figure 1. Recommended omalizumab dosing precluded obese asthma patients from receiving medication. Because of high body weight, both patients (arrows) fell outside current manufacturers' dosing guidelines.

patients were given the maximal recommended omalizumab dose of 375 mg subcutaneously every 2 weeks and are currently still receiving treatment.

Table 3 indicates the improvements in clinical symptoms during the first year of omalizumab therapy in the 2 asthmatic patients. Clinical asthma disease activity is rated based on National Heart, Lung, and Blood Institute Expert Panel 2 asthma guidelines at every visit for all patients treated by our division. During the first year of treatment with omalizumab, both patients were found to have significantly fewer clinic visits with asthma symptoms consistent with moderate to severe persistent severity and significantly more visits with asthma symptoms consistent with mild persistent and mild intermittent severity. In the year preceding omalizumab therapy, neither patient achieved complete asthma control at any visit; patient 1 achieved complete asthma control at the end of the first year of omalizumab treatment (Fig 2 and Table 3). The asthma disease activity of patient 2 improved, although the FEV<sub>1</sub> remained below 80% of predicted. Both patients

required fewer systemic steroid rescues while receiving omalizumab compared with the prior year. The ICS dose was decreased in patient 1 (from 1,880 µg/d to 1,000 µg/d of fluticasone), but reduction in ICS dose in patient 2 resulted in deterioration of symptoms. Neither patient experienced any adverse effects associated with omalizumab injections. Patient 2 experienced mild headaches during initial therapy, which were relieved with premedication using low doses of ibuprofen.

Clinical improvements in these 2 patients are similar to other pediatric asthmatic patients receiving omalizumab within commercial dosing guidelines at LAC+USC Medical Center. Similar improvements occurred in asthma symptoms over time, and variable reductions occurred in ICS dose and systemic steroid rescue courses (data not shown).

## DISCUSSION

We administered omalizumab at maximum recommended doses to 2 patients with severe persistent asthma whose large body weights put them outside current dosing guidelines. During this period both patients had reduced systemic steroids rescue, improvement in asthma disease activity, and increased number of days of asthma control. One patient was able to reduce the ICS requirement. These improvements were similar to those reported in asthmatic patients of similar severity in most omalizumab clinical trials.<sup>1-6</sup>

In pivotal trials, the addition of omalizumab to high-dose ICSs in patients with moderate to severe persistent asthma resulted in a large reduction in asthma exacerbations compared with placebo during steroid stable and steroid reduction phases of the studies. A significant number of these patients were able to reduce the dose of daily required ICSs without deterioration of asthma symptoms, and some were able to be completely weaned off ICSs. Daytime and nighttime asthma symptoms were significantly diminished and quality of life was significantly improved in the active treatment groups. In some patients pulmonary functions improved during the treatment.<sup>1-6</sup> Later studies included patients who were receiving ICSs plus second agents, such as LABAs and LTRAs. Asthma exacerbations, as evidenced by emergency department visits, hospitalizations, systemic steroid rescue, and increased ICS rescue, were significantly reduced in all these subsequent studies. Other secondary outcomes, such as asthma symptoms, quality of life, and lung function, also improved.<sup>8</sup>

In a real-world study, omalizumab given to asthmatic patients whose asthma is not controlled despite normal standard care led to major reductions in asthma exacerbations and ICS use and improvements in asthma symptoms. Similar to the control trials, patients in this real-world study reported major reductions of asthma exacerbations, symptoms, and ICS requirements.<sup>7</sup> These improvements are congruent with improvements experienced by pediatric asthmatic patients given omalizumab at our institution.

Table 3. Clinical Outcomes During Year of Omalizumab Treatment

| Outcomes                        | Patient 1 | Patient 2 |
|---------------------------------|-----------|-----------|
| Reduction in severity*          |           |           |
| Symptoms and PFT results        | Yes†      | No        |
| Symptoms only                   | Yes†      | Yes       |
| Improved PFT results            | NA        | No        |
| ICS dose reduction              | Yes       | No        |
| Reduction in oral steroid burst | Yes       | Yes       |

Abbreviations: ICS, inhaled corticosteroid; NA, not applicable; PFT, pulmonary function test.

\* Complete asthma control was achieved.

† Asthma severity classified using symptoms and pulmonary functions and symptoms alone.

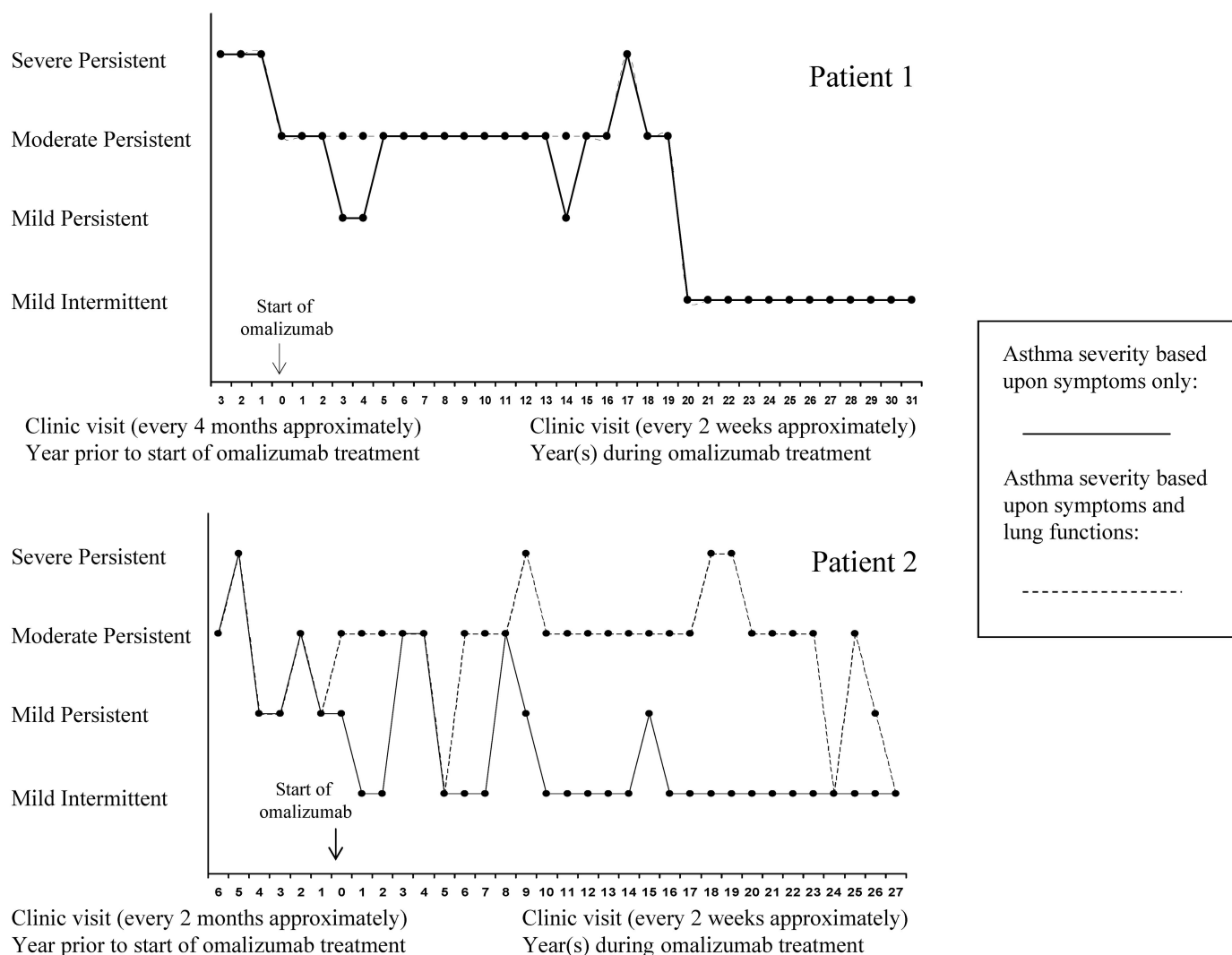


Figure 2. Asthma disease activity of patients 1 and 2 at each clinic visit the year before and during omalizumab treatment. Disease activity was rated using symptoms plus lung functions (broken line) and using symptoms alone (solid line). Patient 1 achieved control of asthma disease activity when rated using both symptoms and lung functions. Patient 2 achieved control of asthma disease activity when only asthma symptoms were used.

To the best of our knowledge, this is the first case report wherein positive response to omalizumab has been shown using multiple parameters to evaluate clinical disease. There was at least one clinical parameter in each individual patient that improved during the period of omalizumab therapy, including reduction of asthma disease activity, reduced systemic steroid rescue, and reduced ICS requirement. Further, we demonstrated improvements in asthma disease activity and asthma control in real time during treatment with omalizumab.

When assessing the effectiveness of omalizumab, large controlled clinical trials usually focus on primary and several secondary end points. Clinical evaluation of asthma is however based on multiple criteria, including day and night

symptoms, rescue inhaler use, peak flow variability, and pulmonary functions. Asthma control is evaluated with these criteria in addition to disease exacerbations. Thus, a significant number of patients may be identified as nonresponders if they are found to not have improvements in the narrow defined set of end points. However, they may still have attenuation of their asthma when more global assessments are measured. For instance, patients who may not have reduction in exacerbations or reductions in ICSs may be deemed as nonresponders. These patients may still have benefited from omalizumab with improvement in disease activity, such as improvement from severe persistent disease activity to mild intermittent activity. Patients who achieve asthma control with disease activity consistent with mild

intermittent symptoms have been shown to have improved quality of life.<sup>15,16</sup>

A worldwide parallel increase in the incidence of asthma and obesity has been seen in recent decades. A strong association exists between obesity and asthma, although studies have not conclusively demonstrated a casual relationship between the 2 disease states. It is unclear whether asthma severity is more severe in obese patients, although it is likely that these patients respond to therapy in a similar fashion to their nonobese counterparts. Nonetheless, from logical inference a number of obese asthmatic patients with severe disease should exist. A significant number of these patients may not optimally respond to standard therapy, such as high-dose ICSs, LABAs, and/or LTRAs, similar to nonobese asthmatic patients. Increasing evidence demonstrates variability in response to controller agents in asthmatic patients.<sup>17,18</sup> Whether omalizumab is therapeutically effective in these nonresponders or partial responders is unknown; however, omalizumab has been shown to reduce asthma morbidity and improve asthma symptoms in patients who are already receiving standard therapy in real-world studies.<sup>7</sup> Thus, it is likely that obese patients with difficult-to-control asthma will also respond to this agent.

Subcutaneous injection of omalizumab results in formation of IgE-anti-IgE IgG complexes, resulting in reduction of total serum IgE levels. When omalizumab is administered according to current manufacturer's guidelines, there is a resultant reduction in the level of free IgE to below 10 IU/L regardless of initial total serum IgE level.<sup>19</sup> It is unknown whether administration of the maximum dose of omalizumab in patients with body weights that fall outside dosing guidelines results in similar IgE reduction; however, because anti-IgE is not deposited in adipose tissue, it is likely that the omalizumab pharmacokinetics in patients who weigh more than 150 kg because of excessive adipose tissue are similar to those of patients with ideal body weights. Therefore, it is possible that significant attenuation of serum IgE results with this strategy.

In this case report, we show that omalizumab therapy administered to 2 patients with severe persistent asthma whose body weight precluded them from receiving omalizumab based on current dosing guidelines experienced significant improvements in asthma symptoms and other disease-related measures. This finding provides rationale for clinical studies designed to evaluate the effectiveness of omalizumab on obese patients and pharmacologic studies aimed at determining optimal omalizumab dosing and IgE reduction in these patients.

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