

# Omalizumab and asthma control in patients with moderate-to-severe allergic asthma: A 6-year pragmatic data review

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## ABSTRACT

Controlled clinical trials have shown the recombinant humanized monoclonal anti-IgE antibody omalizumab to improve asthma control and reduce symptom exacerbations in patients with moderate-to-severe allergic asthma who remain clinically unstable despite optimal medical therapy. An objective retrospective review compared clinical experience with the data reported in the controlled studies. Data tracking for 167 patients progressively enrolled between 2003 and 2010 treated with omalizumab included symptoms, forced expiratory volume at 1 second (FEV<sub>1</sub>), systemic steroid bursts, and need for short-acting bronchodilator rescue measured at the start of therapy; 3, 6, and 12 months after starting treatment, and yearly thereafter. Exacerbations were compared for the 12 months before and the 12 months after starting treatment in a subgroup of patients. Asthma control improved with omalizumab over time (up to 6 years) as indicated by fewer symptoms and less need for rescue medication ( $p < 0.001$  for both). FEV<sub>1</sub> remained stable. The number of patients reporting asthma exacerbations requiring urgent care decreased by 49% during the first 12 months of treatment ( $p \leq 0.01$ ), and significant reductions in exacerbations were also evident when measured by hospitalizations or systemic corticosteroid bursts ( $p < 0.001$  for both). This is the first long-term pragmatic review of omalizumab. Our clinical experience (up to 6 years in some patients) supports the results of earlier controlled studies, confirming the usefulness of adding omalizumab to the long-term management of patients with difficult-to-treat disease who suffer from persistent symptoms despite optimal therapy with medications.

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The recombinant humanized monoclonal anti-IgE antibody, omalizumab (Xolair; Genentech, Inc., South San Francisco, CA) was approved in the United States in the fall of 2003 for the treatment of adolescents and adults with moderate-to-severe or severe allergic asthma and symptoms that are inadequately controlled with inhaled corticosteroids (ICSs). Its approved indication is for patients  $>12$  years of age who have serum IgE levels of 30–700 IU/mL.<sup>1</sup> These are patients with uncontrolled asthma, who—despite optimal treatment per current guidelines—continue to have exacerbations requiring multiple urgent care visits and even hospitalizations, over the course of a year.<sup>2,3</sup>

Omalizumab is administered by subcutaneous injection, and its efficacy and safety have been established in a number of studies.<sup>4–11</sup> In three large prospective studies of up to 28 weeks, omalizumab produced statistically significant reductions in the rate of clinically significant asthma exacerbations compared with placebo, along with improvements in asthma symptom scores.<sup>4–6</sup> The

changes were also reflected in less use of rescue medications, including short-acting  $\beta$ -agonists (SABAs) and bursts of oral corticosteroids. These data are supported by the results of a smaller randomized, double-blinded trial<sup>10</sup> and a randomized, open-label study in patients with moderate-to-severe asthma.<sup>11</sup> The long-term benefits of continuing treatment with omalizumab were shown in extensions of the trials for up to 24 weeks.<sup>7–9</sup>

At the time of its approval in 2003, The William Storms Allergy Clinic began using omalizumab for certain moderate-to-severe asthma patients. Because this was a new form of therapy, we decided to perform a “pragmatic review”—an ongoing observational retrospective assessment limited to patient data within our clinic.<sup>12</sup> The goal was to determine if our clinical experience was the same or different from the data generated in the double-blinded placebo-controlled trials that were used for Food and Drug Administration submission.<sup>5,6,10</sup> Data tracking was instituted for patients who were put on omalizumab, with several outcomes measured at the start of therapy; 3, 6, and 12 months after starting treatment; and yearly thereafter. This is the first long-term pragmatic assessment of the efficacy of omalizumab and the only one that has followed patients for up to 6 years. The initial findings are reported here.

## METHODS

### Patient Evaluations

All patients who received omalizumab in our clinic between 2003 and 2010 were entered into a database.

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**Table 1 Inclusion criteria**

Asthma not controlled\* despite optimal therapy with inhaled corticosteroids with or without long-acting bronchodilators  
 Previously shown positive allergen sensitivity by skin or serum testing to at least one common perennial allergen clinically assessed and judged to contribute substantially to the patient's symptoms  
 Aged  $\geq 12$  yr  
 Total serum IgE  $\geq 30$  to  $\leq 700$  IU/mL

\*As defined by the National Heart, Lung, and Blood Institute Guidelines.<sup>13</sup>

The data included here are for those patients who met the criteria defined in Table 1.

Patients were seen by a clinician at the start of therapy; at 3, 6, and 12 months after beginning therapy; and at least yearly thereafter. At each visit, a history was obtained and a physical examination was performed. Symptoms were assessed and pulmonary function was measured by spirometry. The patient was asked about exacerbations, including episodes requiring urgent care (either emergency department [ED] or after-hours office visits) or hospitalizations, need for bursts of systemic corticosteroids, and rescue medication use (puffs per week of SABA), and they completed the Asthma Control Test (ACT). The ACT was used as a surrogate measure for the severity of asthma symptoms and their impact on the patient's daily life.<sup>13</sup>

Patients who had asthma exacerbations between their regularly scheduled omalizumab follow-up visits were seen on an acute basis and treated accordingly.

This study was exempt from Institutional Review Board approval according to the Code of Federal Regulations, Title 21, Chapter 1, Section 50 (Protection of Human Subjects).

### Statistical Methodology

Statistical analyses were performed on chart data from those patients deemed "evaluable" according to the criteria listed (Table 1). Patients were included in the analyses if they had both a baseline and postbaseline assessment (at 1 year and/or 3 years) for any of the outcomes assessed. The parameter of interest was a patient's change from baseline over time for each assessed outcome.

Asthma exacerbations were evaluated by urgent care visits (after-hours clinic and ED) and hospitalizations during the year before omalizumab and the 1st year of treatment. The data were collected by clinic records and patient histories. Data for the number of systemic steroid bursts were collected for the same time periods in the same manner. Changes in rescue medication (SABA) were evaluated by comparing use at the start of omalizumab treatment to current use (defined as use as of December 2010 or the patient's last visit). SABA use included both metered-dose inhalers and nebu-

**Table 2 Demographics and baseline characteristics for evaluable patients ( $n = 167$ )**

| Variable    | Mean (range)   |
|-------------|----------------|
| Age (yr)    | 52.0 (14–82)   |
| Weight (kg) | 84.3 (50–185)  |
| IgE (IU/mL) | 194.1 (32–670) |

lized formulations for which the dose was adjusted to metered-dose inhaler-equivalent puffs.

ACT and forced expiratory volume at 1 second (FEV<sub>1</sub>) data were analyzed with respect to changes from baseline at 1- and 3-year follow-up. Six-year follow-up data were presented if available but were not required for inclusion in the evaluable population.

Demographic and baseline characteristics were summarized using descriptive statistics. Changes from baseline and percent changes from baseline for each applicable time point were assessed using summary statistics based on parametric testing, with patients serving as their own controls. The statistical analyses were conducted using SAS software Version 9.2 (SAS Institute, Inc., Cary, NC). Tests for normality were included. The exacerbation data, including number of exacerbations, number of urgent care visits, and hospitalizations were evaluated using the *t*-test for related measures.

### RESULTS

A total of 167 patients met the criteria for evaluation, 113 women and 54 men (Table 2). Patient numbers decreased over time primarily because of the normal "drop-out" that occurs in clinical practice. The three main reasons for discontinuation were (1) expense and/or insurance issues, (2) moving and/or transferring to other clinics (for which arrangements were made regarding omalizumab treatment), and (3) efficacy. A total of 16 patients chose to discontinue treatment because of efficacy, 9 (5.4%) because of lack of efficacy within the first 2 years of treatment. The other 7 (4.2%) patients requested stopping treatment (all within 3 years of starting omalizumab) because they felt they had improved to such an extent that they wanted to continue only with their regular medications.

Table 3 Exacerbations in the year before treatment and after 12 mo of omalizumab in 69 patients for whom data was available

| Exacerbation Group                               | No. Patients Who Had One or More Exacerbation in the Year before Treatment (n) | Year before Omalizumab                                |                   | Year after Omalizumab                                 |                               |
|--------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------|-------------------|-------------------------------------------------------|-------------------------------|
|                                                  |                                                                                | Total No. Exacerbations for Group (range per patient) | Per Patient Rate* | Total No. Exacerbations for Group (range per patient) | Per Patient Rate <sup>#</sup> |
| Total                                            | 60                                                                             | 253 (1–18)                                            | 4.21              | 63 (0–7)                                              | 1.05 $\mathbb{I}$             |
| Exacerbations requiring urgent care <sup>#</sup> | 46                                                                             | 85 (1–14)                                             | 4.02              | 21 (0–3)                                              | 0.46 $\mathbb{S}$             |
| Exacerbations resulting in hospitalization       | 27                                                                             | 83 (1–6)                                              | 3.07              | 5 (0–1)                                               | 0.19 $\mathbb{I}$             |

\*No. exacerbations  $\div$  n (defined in table).

<sup>#</sup>After-hours clinic visit or emergency department visit.

$\mathbb{S}p \leq 0.01$ .

$\mathbb{I}p < 0.001$ .

### Asthma Exacerbations

Asthma exacerbations were evaluated in a subgroup of 69 patients (Table 3). Of these patients, 60 had at least one exacerbation (range, 1–18) with a group total of 253 exacerbations in the year before starting omalizumab (rate per patient, 4.21). During the 1st year of treatment, the group total dropped to 63 exacerbations (range, 0–7; rate per patient, 1.05;  $p < 0.001$ ); and within that group of 60, 32 patients had no exacerbations. Exacerbations requiring urgent care and/or hospitalizations also decreased with treatment.

Thirty-seven patients reporting urgent care usage in the year before omalizumab had two or more exacerbations, with a per patient rate in this subgroup of 5.43. After 1 year of treatment, the rate dropped to 0.68 ( $p < 0.001$ ); 25 of these patients had no exacerbations after starting omalizumab.

One outlier was not included in the analysis. This patient reported 29 exacerbations requiring urgent care in the year before starting omalizumab and 4 during the initial 12 months of treatment.

### Bursts of Systemic Corticosteroid

Fifty-eight patients had used bursts of systemic corticosteroids in the year before starting omalizumab. The mean number of bursts was 5.1, which decreased to a mean of 1.1 in the 12 months after omalizumab treatment ( $p < 0.0001$ ; Fig. 1).

### Asthma Symptoms Measured by ACT Scores

ACT scores increased by 58.4% in year 1, approaching normal (score = 20; Fig. 2). After 3 years of treatment, ACT scores had increased by 77.8% and were in

Mean No. Systemic Steroid Bursts

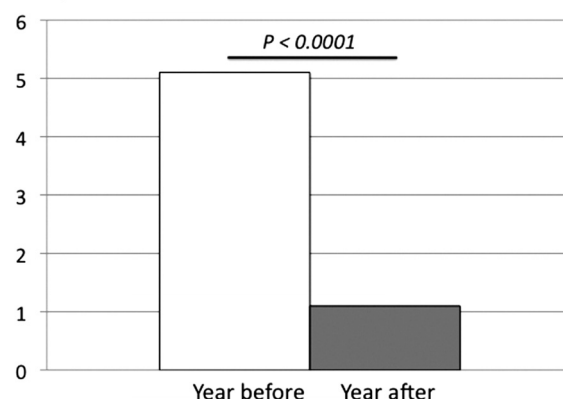


Figure 1. Mean number of systemic steroid bursts in the year before and after starting omalizumab in patients who reported using steroid bursts at baseline (n = 58).

the normal range ( $\geq 20$ ). Only 13 patients remained available for evaluation at 6 years of treatment, but the ACT scores remained in the normal range (mean, 22.69, a 96.4% increase over baseline).

### Rescue Medication

At the initiation of omalizumab treatment patients reported using ~23.0 puffs of SABA per week. At the conclusion of data tracking, patients were using 9.9 puffs/week, a statistically significant reduction of 57.0% ( $p < 0.0001$ ).

### Forced Expiratory Volume at 1 Second

At baseline the patients had a mean FEV<sub>1</sub> of 66.8% predicted. This increased to 74.9% predicted ( $p < 0.0001$ ) after

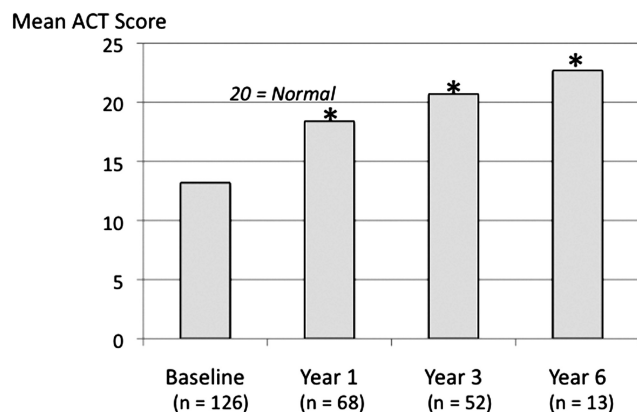


**Figure 2.** Mean Asthma Control Test (ACT) scores over time after starting omalizumab. A score of 20 is considered normal \* $p < 0.001$  vs. baseline.<sup>13</sup>

12 months of omalizumab therapy. At 3 years after starting treatment, FEV<sub>1</sub> was 69.8% predicted ( $p = \text{NS}$ ).

## DISCUSSION

Pragmatic trials are designed to answer important questions affecting clinical practice in a manner that takes advantage of a real-world/real-time setting.<sup>12</sup> For this pragmatic assessment, the question was, does adding omalizumab to the treatment of patients with moderate-to-severe allergic asthma improve asthma control to a degree that will make a difference in terms of morbidity and associated outcomes (e.g., asthma exacerbations and urgent care usage)? Prevention of asthma exacerbations is a critical goal of disease management, but complete control of asthma episodes becomes increasingly difficult in patients with more severe disease.<sup>14</sup> Data from controlled clinical trials have shown that adding omalizumab to a patient's current therapy significantly reduced the likelihood of asthma exacerbations including episodes requiring urgent care (ED visits and after hours office visits) and/or hospitalizations.<sup>4–8,11,15–17</sup> The data reported here support those findings (Table 4).

The patients included here, like those in the earlier controlled studies, were allergic asthmatic patients, who were symptomatic despite optimal therapy according to current guidelines. As shown in Table 4, all studies, including this one, reported that using omalizumab resulted in significant reductions in exacerbations requiring urgent care as well as substantial reductions in the per patient exacerbation rates. This pragmatic review found a better rate of improvement compared with the controlled clinical trials in terms of the percentages of patients with at least one asthma exacerbation requiring an ED or acute care visit: a 46.4% reduction versus reductions of between 9 and 18% in the clinical trials. This is not surprising, because pragmatic studies often show better rates of improve-

ment compared with clinical trials.<sup>12</sup> The variability in outcomes probably reflects the different methods for capturing data as well as differences in patient populations and duration of treatment. Controlled efficacy studies recruit patients that meet specific criteria to assess specific outcomes. In contrast, patients included in pragmatic studies come from a variety of settings, creating a more heterogeneous mix.<sup>12</sup> Furthermore, all of the earlier studies compared two groups of patients—controls (placebo + current therapy or current therapy alone) versus omalizumab. We looked at the same patients before using omalizumab (the control) and after starting treatment. Despite these differences, the trends are the same and we believe the reductions in exacerbations observed with omalizumab—regardless of how studied—to be clinically relevant. Supporting this is the fact that patients in the double-blinded, placebo-controlled studies continued to have fewer exacerbations even when ICSs were reduced.<sup>5,6,15</sup>

A recently published study reported 7% fewer patients with exacerbations after 48 weeks of omalizumab, a 25% decrease in the per patient exacerbation rate compared with placebo.<sup>18</sup> The protocol-defined asthma exacerbation in that trial was worsening asthma symptoms requiring treatment with systemic corticosteroids for  $\geq 3$  days or a  $\geq 20$ -mg increase in oral corticosteroid dose for patients requiring daily oral corticosteroids. Using that definition of exacerbation, our patients also had significantly fewer exacerbations after starting treatment.

Fewer hospitalizations after starting omalizumab were reported by the patients reviewed, again supporting the data from controlled studies.<sup>4,11</sup> As for exacerbations, the overall reduction in hospital rate per patient was greater in this observational review (~89%) than in the clinical trials (between 28 and 59%), which probably reflects the differences between pragmatic and controlled studies as described previously. Hospitalizations reflect the most severe exacerbations, occurring in a limited number of patients. At least one double-blinded, placebo-controlled trial did not report any change in hospitalization rates with omalizumab.<sup>9</sup>

Using omalizumab led to long-term improvements in symptoms concomitant with less use of rescue SABA, similar to earlier observations reported in the controlled studies.<sup>4–7,11,15</sup> We used the ACT test as an easy-to-use and convenient surrogate to gather information about how symptoms affected these patients before and after starting omalizumab. Treatment with omalizumab normalized the patients' ACT scores over time, and the change was maintained—up to 6 years in some cases.

The lack of substantial change in FEV<sub>1</sub> is not surprising. At the start of treatment, patients had been using other medications, and although their asthma was labile as determined by symptoms and exacerbations, in some cases FEV<sub>1</sub> was in the mild range. In this analysis, we also included patients who had FEV<sub>1</sub> scores of  $>80\%$  (that

Table 4 Patients experiencing at least one asthma exacerbation episode requiring ED or acute care visit

| Study                                | Description                                                   | n                                              | Patients with Episodes (%)        |                                                             | Rate per Patient                                                               |
|--------------------------------------|---------------------------------------------------------------|------------------------------------------------|-----------------------------------|-------------------------------------------------------------|--------------------------------------------------------------------------------|
|                                      |                                                               |                                                | Control                           | Omalizumab                                                  |                                                                                |
| Milgrom <i>et al.</i> <sup>14</sup>  | DB, PC; SSP: 12 weeks, SRP: 8 wk                              | O, high dose:* 106; O, low dose:* 106; Pl: 105 | 45%                               | High dose: 30% ( $p = 0.03$ ); low dose: 28% ( $p = 0.01$ ) | Not reported                                                                   |
| Busse <i>et al.</i> <sup>6</sup>     | DB, PC; SSP: 16 weeks, SRP: 12 wk                             | O: 268; Pl: 257                                | SSP: 23.3%; SRP: 32.2%            | SSP: 14.6% ( $p = 0.0009$ ); SRP: 21.3% ( $p = 0.0004$ )    | SSP: Pl, 0.54; O, 0.28 ( $p = 0.006$ ); SRP: Pl, 0.66; O, 0.39 ( $p = 0.003$ ) |
| Soler <i>et al.</i> <sup>5</sup>     | DB, PC; SSP: 16 weeks; SRP: 12 wk                             | O: 274; Pl: 272                                | SSP: 30.5%; SRP: 29.8%            | SSP: 12.8% ( $p < 0.001$ ); SRP: 15.7% ( $p < 0.001$ )      | SSP: Pl, 0.66; O, 0.28 ( $p < 0.001$ ); SRP: Pl, 0.75; O, 0.36 ( $p < 0.001$ ) |
| Buhl <i>et al.</i> <sup>7</sup>      | 24 wk extension trial (see Soler <i>et al.</i> <sup>5</sup> ) | O: 254; Pl: 229                                | 40.6%                             | 24.0% ( $p < 0.001$ )                                       | Pl, 1.14; O, 0.48 ( $p < 0.001$ )                                              |
| Lanier <i>et al.</i> <sup>8</sup>    | 24 wk extension trial (see Busse <i>et al.</i> <sup>6</sup> ) | O: 245; Pl: 215                                | 42.8%                             | 31.8% ( $p = 0.015$ )                                       | Pl, 0.83; O, 0.60 ( $p = 0.023$ )                                              |
| Ayres <i>et al.</i> <sup>11</sup>    | OL; 12 mo                                                     | O: 206; Pl: 106                                | 50.6%                             | 33.5% ( $p = 0.007$ )                                       | Not reported                                                                   |
| Humbert <i>et al.</i> <sup>4</sup>   | DB, PC; 28 wk                                                 | O: 245; Pl: 215                                | Not reported as no. or % patients |                                                             | Pl, 0.43; O, 0.24 ( $p = 0.038$ )                                              |
| Niven <i>et al.</i> <sup>9</sup>     | OL; 12 mo                                                     | O: 115; C: 49                                  | 25%                               | 16.8% (12.9% for O responders)#                             | C, 3.06; O, 1.26 ( $p < 0.001$ )                                               |
| Storms <i>et al.</i> (current paper) | Pragmatic trial, 12 months§                                   | 69                                             | 66.7%                             | 20.3% ( $p \leq 0.01$ )                                     | C, 4.02; O, 0.46 ( $p \leq 0.01$ )                                             |

All studies involved patients with moderate-to-severe persistent allergic asthma who were inadequately controlled on high doses of ICSs and other medications (e.g., long-acting bronchodilators).

\*High dose = 5.8  $\mu\text{g/kg}$  body weight/ng IgE/mL; low dose = 2.5  $\mu\text{g/kg}$  body weight/ng IgE/mL.

#Identified by  $\geq 0.5$  point improvement in Mini-AQLQ overall score at 27 weeks.

§Patients were compared with themselves, year before using omalizumab (C) vs year after starting omalizumab (O). Data included ED and acute care visits.

C = control; DB = double-blind; ED = emergency department; ICS = inhaled corticosteroid; O = omalizumab; OL = open-label; PC = placebo-controlled; Pl = placebo; pp = per patient; SRP = steroid reduction phase; SSP = steroid stable phase.

were excluded from most clinical trials). However, although the data were not collected, patients reported using less of their maintenance therapy—notably, ICS. Despite those observed reductions, FEV<sub>1</sub> did not change. FEV<sub>1</sub> is a complex measure and, perhaps, not the best means to assess the ongoing clinical benefit of omalizumab for these types of patients.<sup>19</sup>

### Other Limitations

In an observational study data are collected on real-world clinic patients and, as such, are affected by the usual things that happen in a clinic practice. For instance, during the 1st year ~40 patients were started on omalizumab, but by year 6 several had moved to

other locations, and we do not have follow-up data on them despite the fact that arrangements were made to transfer care as appropriate.

Additionally, the variables that can impact patient outcomes in practice raise the question of whether the observed improvements were caused by omalizumab alone. That is a difficult question to answer. However, our patients were well documented with regard to disease severity and treatment both before and during the observational period. Although not yet reported, usage of regular ICS with or without long-acting  $\beta$ -agonists was monitored throughout. For most patients, maintenance therapy either stayed the same or decreased; and, as indicated, some patients believed that their symptoms

had improved to such a degree that they requested discontinuing omalizumab. The medication usage data are being evaluated in greater detail, including a “response to therapy” analysis for individual patients that we hope will allow us to tease out some of the variables that might contribute to efficacy or lack thereof.

A related issue is that our comparisons were made only to the year before treatment, such that the observed improvements could reflect regression to the mean or spontaneous improvement related to the variability of the disease. This is probably not the case for these patients who had a history of difficult-to-control asthma and who appear to match those in previous controlled clinical trials. Nonetheless, the data do not permit determination of the degree of improvement actually due to treatment.

Other limitations related to declining patient numbers over time and the lack of non-omalizumab controls within the clinic may be addressed by the results of the Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate-to-Severe Asthma (EXCELS). This large, prospective study was designed to evaluate the long-term (5-year) clinical safety of omalizumab, including malignant tumors and other serious adverse events.<sup>20</sup> Secondary outcomes include the effectiveness of omalizumab in patients with moderate-to-severe persistent asthma assessed in a real-world clinical practice setting using measures similar to those reported here: ACT score, asthma-related health care usage, and need for systemic steroid bursts. The EXCELS trial in 7951 patients (omalizumab, 5041; non-omalizumab, 2886) is ongoing.<sup>20</sup>

In summary, this observational, retrospective data review found that adding omalizumab to the treatment of patients with uncontrolled moderate-to-severe allergic asthma significantly reduced exacerbation rates and associated urgent care visits and hospitalizations and also improved measures of asthma control. This is the first pragmatic evaluation of omalizumab and the only long-term assessment of its size conducted for >2 years. Our observations are similar to those reported in controlled clinical trials and confirm the usefulness of adding omalizumab to the long-term management of patients with difficult-to-treat disease who suffer from persistent symptoms despite “optimal” therapy with standard of care.

## REFERENCES

1. Genentech USA, Inc., and Novartis Pharmaceutical Corp. Xolair (omalizumab) prescribing information. Genentech USA, Inc., South San Francisco, CA, and Novartis Pharmaceutical Corp., East Hanover, NJ; 7/2010.
2. Holgate S, Buhl R, Bousquet J, et al. The use of omalizumab in the treatment of severe allergic asthma: A clinical experience update. *Respir Med* 103:1098–1113, 2009.
3. Rodrigo GJ, Neffen H, and Castro-Rodriguez JA. Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for adults and children with asthma: A systematic review. *Chest* 139:28–35, 2011.
4. Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 60:309–316, 2005.
5. Soler M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 18:254–261, 2001.
6. Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 108:184–190, 2001.
7. Buhl R, Soler M, Matz J, et al. Omalizumab provides long-term control in patients with moderate-to-severe allergic asthma. *Eur Respir J* 20:73–78, 2002.
8. Lanier BQ, Corren J, Lumry W, et al. Omalizumab is effective in the long-term control of severe allergic asthma. *Ann Allergy Asthma Immunol* 91:154–159, 2003.
9. Niven R, Chung KF, Panahloo Z, et al. Effectiveness of omalizumab in patients with inadequately controlled severe persistent allergic asthma: An open-label study. *Respir Med* 102:1371–1378, 2008.
10. Holgate ST, Chuchalin AG, Herbert J, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy* 34:632–638, 2004.
11. Ayres JG, Higgins B, Chilvers ER, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. *Allergy* 59:701–708, 2004.
12. Ware JH, and Hamel MB. Pragmatic trials—Guides to better patient care? *N Engl J Med* 364:1685–1687, 2011.
13. National Heart, Lung, and Blood Institute. Guidelines for the diagnosis and management of asthma. National Asthma Education and Prevention Program, Expert Panel Report 3. National Heart, Lung, and Blood Institute, Washington, D.C., 2007. Available online at [www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf](http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf); accessed August 6, 2011.
14. Broder MS, Chang EY, Kamath T, and Sapra S. Poor disease control among insured users of high-dose combination therapy for asthma. *Allergy Asthma Proc* 31:60–67, 2010.
15. Milgrom H, Fick RB Jr, Su JQ, et al. Treatment of allergic asthma with monoclonal anti-IgE antibody, rhuMAB-E25 Study Group. *N Engl J Med* 341:1966–1973, 1999.
16. Bousquet J, Cabrera P, Berkman N, et al. The effect of treatment with omalizumab on anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy* 60:302–308, 2005.
17. Bousquet J, Rabe K, Humbert M, et al. Predicting and evaluating response to omalizumab in patients with severe allergic asthma. *Respir Med* 101:1483–1492, 2007.
18. Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy. *Ann Intern Med* 154:573–582, 2011.
19. Patil SU, and Long AA. The usefulness of biomarkers of airway inflammation in managing asthma. *Allergy Asthma Proc* 31:259–268, 2010.
20. Long AA, Fish JE, Rahmaoui A, et al. Baseline characteristics of patients enrolled in EXCELS: A cohort study. *Ann Allergy Asthma Immunol* 103:212–219, 2009. □

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