Omalizumab as Add-on Therapy to Inhaled Steroids for Asthma

Summary

- In the US, subcutaneous administration of omalizumab is indicated for adults and adolescents (age ≥12 years) with allergic asthma that is moderate to severe and inadequately controlled with inhaled corticosteroids.
- In placebo-controlled trials, omalizumab reduces asthma exacerbations and the need for inhaled steroids in this group.
- The value of omalizumab to patients with severe asthma (e.g., refractory asthma) has yet to be proven.
- Data are lacking on the efficacy of omalizumab compared to add-on therapies such as inhaled long-acting beta-2 agonists or anti-leukotriene agents.
- Further evaluation on omalizumab needs to be done in the pediatric population.

The Technology

Omalizumab is a humanized monoclonal antibody that binds to immunoglobulin E (IgE) and blocks interactions between IgE and receptors on mast cells and basophils. This is thought to inhibit the release of inflammatory mediators such as histamine, leukotrienes and cytokines. It may also indirectly lessen the activity of mast cells and basophils. Omalizumab was jointly developed by Novartis Pharma AG, Genentech, Inc. and Tanox, Inc. It is marketed in the US by Genentech and Novartis Pharmaceuticals Corporation.

Regulatory Status

Omalizumab was approved in the US for adults and adolescents (≥12 years of age) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial Aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. It was also approved in Australia for allergic asthma and seasonal allergic rhinitis. A marketing application is under review by Health Canada.

Asthma is a chronic inflammatory disorder of a person’s airways. In the last 25 years, it has become more prevalent in children and young adults. Exposure to an allergen (e.g., dust, mould, pollen) may contribute to asthma pathogenesis in up to 90% of patients. Over 2.2 million Canadians have been diagnosed with asthma (12.2% of children and 6.3% of adults). Asthma severity is often classified according to the frequency of symptoms and options for treatment. Patients with moderate to severe asthma have daily symptoms that are usually controlled with a moderate to high dose of inhaled corticosteroid (ICS), with or without additional therapy.

Current Practice

Canadian guidelines suggest that asthma be managed with symptom relievers and symptom controllers. Short-acting beta-2 agonists are used to relieve acute asthma symptoms, while ICS is the controller of choice. Leukotriene receptor antagonists (LTRAs) may also be used as controllers alone, but they are less effective. When one drug is insufficient, a combination of a long-acting beta-2 agonist (LABA) and an ICS is an effective therapy. LTRAs are second-line alternatives to LABAs as add-on therapy. Theophylline is another possibility. Oral steroids are recommended for patients with severe asthma or to treat acute exacerbations.
The Evidence

The efficacy and safety of omalizumab need to be compared to those of current add-on therapies.7 (See the 2003 Canadian Asthma Consensus Report, Can Resp J, In Press for May 04 issue.)

Four placebo-controlled8-11 trials [i.e., studies 008, 009, 010 and 011 in the Food and Drug Administration (FDA) report12] evaluated the efficacy and safety of omalizumab in patients having a positive skin test reaction to a perennial aeroallergen; having increased IgE serum levels; having asthma for at least one year; and requiring daily ICS. All four studies lasted 32 weeks. They were divided equally into a steroid-stable phase, during which steroid dosages were kept stable; and a steroid-reduction phase (Table 1).

Asthma exacerbations: A meta-analysis of two studies8,9 of adults with moderate to severe allergic asthma showed that during both treatment phases, omalizumab significantly reduced the number of patients with exacerbations (Table 1) and the mean number of exacerbations per subject, compared with placebo.8,9 In the pediatric study, omalizumab achieved the same results but only during the steroid-reduction phase (Table 1).10 In a study involving patients with severe asthma (defined by their baseline dose of ICS11), omalizumab had no significant effect on either measure in either treatment phase (Table 1).11

Need for steroids: In three studies,8-10 omalizumab, compared with placebo, allowed a higher proportion of subjects to stop using ICS (Table

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean Baseline FEV1 (% predicted)</th>
<th>Asthma Severity</th>
<th>Number of Patients</th>
<th>Treatment Phase</th>
<th>Number (% of Patients with ≥1 Exacerbations Observed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>008 (Busse et al. 2001)8</td>
<td>67.95%</td>
<td>Adults with MSA</td>
<td>268</td>
<td>Stable steroid</td>
<td>30 (11) vs 47 (18), RRR=57.3% (95% CI: 39.1-66.6) NNT=14 (8.98)</td>
</tr>
<tr>
<td>009 (Soler et al. 2001)9</td>
<td>69.85%</td>
<td>Adults with MSA</td>
<td>274</td>
<td>Stable steroid</td>
<td>27 (10) vs 63 (23), RRR=57.3% (95% CI: 35.7-72.4) NNT=8 (5.14)</td>
</tr>
<tr>
<td>Meta-analysis of 008 and 009</td>
<td></td>
<td></td>
<td>542</td>
<td>Steroid reduction</td>
<td>26 (10) vs 44 (16), RRR=57.3% (95% CI: 8.63-81.0) NNT=15 (8.94)</td>
</tr>
<tr>
<td>010 (Milgrom et al. 2001)10</td>
<td>84.33%</td>
<td>Children with MSA</td>
<td>255</td>
<td>Stable steroid</td>
<td>57 (11) vs 110 (21), RRR=57.3% (95% CI: 32.6-75.2) NNT=10 (7.17)</td>
</tr>
<tr>
<td>011 ICS-only subgroup (Holgate et al. 2004)11</td>
<td>64.41%</td>
<td>Adults with SA</td>
<td>126</td>
<td>Stable steroid</td>
<td>13 (10) vs 15 (13), RRR=57.3% (95% CI: 33.73-66.59) NNT=6 (4.14)</td>
</tr>
</tbody>
</table>

1 Adults age 12 to 75 years and children age 6 to 12 years. Omalizumab was given subcutaneously every two or four weeks [dose of 0.016 mg/kg/IgE (IU/mL) according to body weight and baseline IgE concentration].

2 Exacerbations defined as worsening of symptoms, requiring treatment with oral steroids or doubling the baseline dose of inhaled steroid (intention-to-treat population analysis). ³Significant effect.

BDP=beclomethasone dipropionate; CI=confidence interval; ICS=inhaled corticosteroid; FP=fluticasone; MSA=mild to moderate; NE=not estimable with confidence; NNT=number needed to treat; RRR=relative risk reduction; SA=severe asthma; FEV1=forced expiratory volume in one second.

The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) is a non-profit organization funded by the federal, provincial and territorial governments. (www.ccohta.ca)
2). The median ICS dose was also lower with omalizumab treatment (25% to 33% reduction as compared to placebo, p<0.01). In patients with severe asthma, however, omalizumab treatment did not allow a significant number of patients to stop using ICS (Table 2) and only slightly reduced the steroid dose (50% with placebo versus 60% for omalizumab), though this is statistically significant. This latter study also included a subgroup of 95 patients using systemic steroid. There was no significant reduction in their steroid dose or asthma exacerbations (unpublished, but see FDA report).

Other outcomes: A Cochrane review and meta-analysis of the same trials revealed that, relative to placebo, omalizumab did not improve lung function (neither forced expiratory volume in one second nor peak expiratory flow) and did not significantly reduce the need for rescue beta-2 agonists (<1 puff/day). There was a small, though significant, decrease in asthma symptom scores in all studies but one (the pediatric study). Asthma-related quality of life also improved.

Safety Data
The most serious adverse events reported with omalizumab were malignancies and anaphylaxis. Malignant neoplasms were observed in 20/4,127 patients (0.5%) compared with 5/2,236 control patients (0.2%). A phase IV pharmacovigilance study is underway to determine any association with omalizumab. Anaphylactic reactions were rare but occurred in three patients (<0.1%) within two hours (not immediately) of the first or subsequent administration of omalizumab. There were no other identifiable allergic triggers in two patients.

Administration and Cost
Omalizumab is administered subcutaneously every two or four weeks, based on body weight and baseline IgE concentration. In the US, the wholesale price is US$433 per vial of lyophilized powder for reconstitution. The annual cost per patient is projected to be approximately US$10,000 to US$12,000.

Rate of Technology Diffusion
The high price of this drug could discourage its use; so too could the means of administration, as the subcutaneous route may not appeal to some patients.

Administration by a physician may control some aspects of treatment compliance. The recent incorporation of omalizumab into Global Initiative for Asthma (GINA) guidelines may influence physicians to consider it. The optimal role of omalizumab, however, is not yet defined.

Concurrent Developments
Two drugs have been tested in placebo-controlled phase I and II clinical trials. One is a soluble recombinant interleukin (IL)-4 receptor that blocks IL-4 (responsible for IgE biosynthesis). The other is a monoclonal antibody, keliximab, which is directed against white blood cells.

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Table 2: Incomplete withdrawal from ICS in placebo-controlled studies of omalizumab (Xolair™) in patients with asthma

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Number (% of Patients with Incomplete Steroid Withdrawal a)</th>
<th>RRR (%) (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Xolair</td>
<td>Placebo</td>
<td>Xolair</td>
<td>Placebo</td>
</tr>
<tr>
<td>008</td>
<td>268</td>
<td>257</td>
<td>162 (60.4)</td>
<td>208 (80.9)</td>
</tr>
<tr>
<td>009</td>
<td>274</td>
<td>272</td>
<td>156 (56.9)</td>
<td>219 (80.5)</td>
</tr>
<tr>
<td>Meta-analysis of 008 and 009</td>
<td>542</td>
<td>529</td>
<td>318 (59)</td>
<td>427 (81)</td>
</tr>
<tr>
<td>010</td>
<td>225</td>
<td>109</td>
<td>101 (44.9)</td>
<td>67 (61.5)</td>
</tr>
<tr>
<td>011 ICS-only subgroup¹³</td>
<td>126</td>
<td>120</td>
<td>99 (78.6)</td>
<td>102 (85.0)</td>
</tr>
</tbody>
</table>

aIntention-to-treat analysis. ¹Significant effect. Abbreviations as defined in Table 1.
known as CD4 lymphocytes. They are thought to be responsible for inflammation in asthma. Both drugs have been shown to moderately reduce asthma symptoms.\textsuperscript{16,17}

**Implementation Issues**

The current evidence, though limited, indicates that patients with moderate to severe asthma are most likely to benefit from omalizumab. The value of omalizumab to patients with severe asthma is yet to be proven.\textsuperscript{11,12}

Omalizumab’s safety profile is of concern. Data on the long-term efficacy and safety associated with its chronic use are lacking. Moreover, this drug can only be administered by physicians because of the risk of anaphylaxis.

The future of omalizumab will depend on its cost-effectiveness and its benefit compared to those of proven add-on therapies for moderate to severe asthma,\textsuperscript{4,7} such as ICS and LABA (or their combination product).

**References**


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