Drug Monograph: Omalizumab (XOLAIR®)

LAI Fung Yee, Fiona
LO Elaine Ah Gi
KEI Hoi Wing, Claire
TSE Pui Ling, Kannie
WONG Yin Cheong, Eric

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Abbreviations: IgE, immunoglobulin E; SC, subcutaneous; ICS, inhaled corticosteroid.


Summary

Omalizumab, a recombinant DNA-derived humanized monoclonal antibody attenuates allergic response in patients with allergic asthma. It decreases the unbound serum immunoglobulin E (IgE) levels by forming complexes with it. It also binds with high-affinity IgE receptors on basophils so as to lower the chance of allergic responses. Results of some clinical trials demonstrated that omalizumab administered subcutaneously is a safe and effective treatment for moderate to severe allergic asthma in patients who i) are poorly controlled on conventional therapy, ii) experience adverse effects caused by high-dose or prolonged corticosteroid treatment, or iii) have frequent exacerbations because of poor medication adherence.

Omalizumab can result in mild adverse reaction and is contraindicated in patients having hypersensitive reactions to the drug or Chinese hamster ovary. The high cost associated with omalizumab treatment may be prohibitive for some patients, thereby limiting its utility. Its cost-effectiveness is still under debate [1]. Certainly more randomized, placebo-controlled clinical trials are required to further establish the effectiveness and role of omalizumab in the management of asthma.

Introduction

Omalizumab is a recombinant monoclonal antibody directed against IgE, which is implicated in allergic asthma. Through formation of complexes with IgE, omalizumab is able to reduce the frequency of exacerbation in asthmatics and hence is useful for treating moderate to severe allergic asthma. Subcutaneous (SC) injection is the designed route of administration of omalizumab. The commercial product of Xolair® is presented as a sterile, white, preservative-free, lyophilized powder contained in a single-used vial [2].

Indications

Omalizumab (Xolair®) was approved by FDA in 2003 [3] for treatment of moderate to severe persistent allergic asthma in adults and adolescents (12 years of age and above) who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Evidence showed that it can reduce the number of asthma exacerbations or episodes of airway
constriction that result in cough, breathlessness, and wheezing, however, safety and efficacy have not been established in other allergic conditions [2].

**Evidence-Based Clinical Guidelines**

A search of literature was performed to identify evidence-based clinical guidelines. This included Medline, Embase, the National Guideline Clearinghouse website and other Internet search engines. A few guidelines were identified.

The guideline of the Global Initiative for Asthma [4] suggested Omalizumab can be used for patients with elevated serum levels of IgE in severe allergic asthma which is uncontrolled on inhaled glucocorticosteroids. It is also stated in the guideline of the British Thoracic Society and the Scottish Intercollegiate Guidelines Network [5] that the role of Omalizumab in the stepwise management of asthma is not well established at present but it may be beneficial in specific patients with severe persistent allergic asthma.

Some practitioners suggested that to decide whether to begin the omalizumab therapy, full understanding about the nature of the therapy (i.e. this is a long-term therapy, administered SC every 2 or 4 weeks depending on body weight and baseline IgE level) should be acquired first. They further pointed out that this medication is not prescribed in a traditional manner, but rather a “statement of medical necessity” is completed and sent to a participating specialty pharmacy. This statement of medical necessity (SMN) includes information about the patient, insurance coverage, clinical data, concomitant medications, IgE level, and dosage [6].

**Clinical Studies**

Relatively few clinical trials had been conducted on omalizumab. There were 3 major studies on the use of omalizumab in asthma therapy: STUDY 1 [7], STUDY 2 [8] and STUDY 3 [9]. STUDY 1 and STUDY 2 supported the use of omalizumab in patients with symptomatic allergic asthma despite treatment with ICS and short-acting beta agonists, but results from STUDY 3 showed that omalizumab lacked efficacy in managing these conditions.
**STUDY 1 [7]**

**Conclusion**
The addition of omalizumab to standard asthma therapy is effective in reducing asthma exacerbations and decreases inhaled corticosteroid (ICS) and rescue medication use.

<table>
<thead>
<tr>
<th>STUDY DESIGN</th>
<th>Multi-center, randomized, double-blind, placebo-controlled clinical trial (n = 525).</th>
</tr>
</thead>
<tbody>
<tr>
<td>INCLUSION CRITERIA</td>
<td>Patients aged 12 to 75 yrs with symptomatic allergic asthma despite treatment with ICS and short-acting beta agonists; +ve immediate skin prick test; serum IgE 30-700 IU/mL; FEV1 reversibility of ≥12% within 30 mins after administration of albuterol; baseline FEV1 40-80% of predicted; treatment with ICS for at least 3 months.</td>
</tr>
<tr>
<td>EXCLUSION CRITERIA</td>
<td>Prior exposure or sensitivity to omalizumab; acute URI within 1 month; &lt;3 months of stable immunotherapy; elevated IgE levels for reasons other than atopy; regular treatment with beta-agonists; omalizumab requirement of &gt;750 mg per 4 wks; smoking.</td>
</tr>
<tr>
<td>TREATMENT REGIMEN</td>
<td>Patients were randomized to receive placebo or omalizumab SC every 2 or 4 wks, depending upon baseline IgE level and body weight, for 7 months. Omalizumab dose was approx. 0.016 mg/kg IgE per 4 wks. ICS doses were kept stable over the initial 16 wks of treatment and tapered during a further 12 wk treatment period.</td>
</tr>
<tr>
<td>RESULTS</td>
<td>1. Omalizumab treatment resulted in significantly fewer asthma exacerbations per subject and in lower percentages of subjects experiencing an exacerbation than placebo treatment during the stable steroid phase (0.28 vs 0.54 [p = .006] and 14.6% vs 23.3% [p = .009], respectively) and during the steroid reduction phase (0.39 vs 0.66 [p = .003] and 21.3% vs 32.3% [p = .004], respectively).</td>
</tr>
<tr>
<td></td>
<td>2. Beclomethasone dipropionate reduction was significantly greater with omalizumab treatment than with placebo (median 75% vs 50% [p &lt; .001]), and beclomethasone dipropionate discontinuation was more likely with omalizumab (39.6% vs 19.1% [p &lt; .001]).</td>
</tr>
<tr>
<td></td>
<td>3. Improvements in asthma symptoms and pulmonary function occurred along with a reduction in rescue β-agonist use.</td>
</tr>
</tbody>
</table>
SAFETY

Omalizumab was well tolerated with side effects similar to placebo.

STUDY 2 [8]

Conclusion

Omalizumab therapy safely improves asthma control in allergic asthmatics who remain symptomatic despite regular use of ICSs and simultaneous reduction in corticosteroid requirement.

<table>
<thead>
<tr>
<th>STUDY DESIGN</th>
<th>Multi-center, randomized, double-blind, placebo controlled clinical trial (n = 546).</th>
</tr>
</thead>
<tbody>
<tr>
<td>INCLUSION CRITERIA</td>
<td>Patients aged 12 to 76 yrs with allergic asthma for at least 1 yr; +ve skin prick test; serum IgE 30-700 IU/mL; body weight ≤ 150 kg; baseline FEV1 40-80% of predicted; FEV1 reversibility of ≥ 12% within 30 mins after administration of albuterol; mean total daily symptom score of ≥ 3.0; treatment with ICS for at least 3 months and use of short-acting beta agonists on an as-needed or regular basis.</td>
</tr>
<tr>
<td>EXCLUSION CRITERIA</td>
<td>Use of oral corticosteroids; smoking.</td>
</tr>
<tr>
<td>TREATMENT REGIMEN</td>
<td>Patients were randomized to receive placebo or omalizumab SC every 2 or 4 wks, depending on body weight and baseline IgE, for months. Omalizumab dose was approx. 0.016 mg/kg IgE per 4 wks. ICS doses were kept stable for 16 wks and were progressively reduced over the following 8 wks, with the lowest dose required continued for the next 4 wks.</td>
</tr>
</tbody>
</table>
| RESULTS | 1. Compared to the placebo group, the omalizumab group showed 58% fewer exacerbations per patient during the stable-steroid phase (p<0.001).
2. During the steroid-reduction phase, there were 52% fewer exacerbations in the omalizumab group Vs the placebo group (p<0.001) despite the greater reduction of the beclomethasone dosage on omalizumab (p<0.001). |
| SAFETY | Omalizumab was well tolerated with side effects similar to placebo. |
**STUDY 3 [9]**

**Conclusion**
Omalizumab is not more effective than placebo in reducing asthma exacerbations in patients receiving ICSs with or without oral corticosteroids and/or long-acting beta-agonists.

<table>
<thead>
<tr>
<th>STUDY DESIGN</th>
<th>Multicenter, randomized, double-blind, placebo-controlled clinical trial (n=341).</th>
</tr>
</thead>
<tbody>
<tr>
<td>INCLUSION CRITERIA</td>
<td>Patients aged 12 to 75 yrs with symptomatic allergic asthma, despite treatment with ICS and short-acting beta-agonists with or without oral corticosteroids; FEV1 improvements of at least 12% following beta-agonist administration; serum IgE 30-700 IU/mL.</td>
</tr>
<tr>
<td>EXCLUSION CRITERIA</td>
<td>Smoking</td>
</tr>
<tr>
<td>TREATMENT REGIMEN</td>
<td>Patients were randomized to receive placebo or omalizumab SC every 2 or 4 wks, depending upon body weight and baseline IgE, for 8 months. Omalizumab dose was approximately 0.016 mg/kg IgE per 4 wks. ICS doses with or without oral corticosteroids were kept stable for 16 wks and were progressively reduced over a 16 week period. Long-acting beta agonists were also allowed.</td>
</tr>
<tr>
<td>RESULTS</td>
<td>The percentage of patients with $\geq 1$ exacerbations were similar for both omalizumab and placebo groups during the stable steroid and steroid reduction phase for patients receiving ICS (15.9% versus 15.0% and 22.2% versus 26.7%, respectively). In patients receiving ICS plus oral corticosteroids, the results were also similar in both omalizumab and placebo groups (32.0% versus 22.2% and 42.0% versus 42.2%, respectively.</td>
</tr>
<tr>
<td>SAFETY</td>
<td>Not specified</td>
</tr>
</tbody>
</table>
Besides STUDY 1, 2, 3, there are also some other clinical study and pooled analyses supporting the use of omalizumab in moderate to severe allergic asthma.

**STUDY 4 [10]**

**Conclusion**
Omalizumab reduces the rate of serious asthma exacerbations and the need for unscheduled outpatient visits, emergency room treatment, and hospitalization in patients with moderate-to-severe allergic asthma.

<table>
<thead>
<tr>
<th><strong>Background</strong></th>
<th>Prevention of serious asthma exacerbations is an important therapeutic goal in patients with asthma.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>Investigate the effect of omalizumab (Xolair) on the rate of serious exacerbations during long-term therapy.</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>Pooled analysis was completed of 3 multi-center, randomized, double-blind, placebo-controlled phase III studies with omalizumab in adults/adolescents aged $\geq 12$ yrs ($n = 1071$) and in children aged 6 to 12 yrs ($n = 334$) who required treatment with ICSs for allergic asthma.</td>
</tr>
</tbody>
</table>
| **Results**   | 1. Rate of unscheduled, asthma-related outpatient visits was lower for the omalizumab-treated patients than for the placebo-treated patients, as were asthma-related emergency room visits.  
2. Hospitalizations for asthma were markedly reduced in patients receiving omalizumab. |

**STUDY 5 [11]**

**Conclusion**
In patients with inadequately controlled severe persistent asthma, despite high-dose ICS and long-acting $\beta_2$-agonists therapy, and often additional therapy, omalizumab significantly reduced the rate of clinically significant asthma exacerbations, severe exacerbations and emergency visits. Omalizumab is effective and should be considered as add-on therapy for patients with inadequately controlled severe persistent asthma who have a significant unmet need despite best available therapy.
### Background
Patients with severe persistent asthma who are inadequately controlled despite Global Initiative for Asthma (GINA) 2002 step 4 therapy are a challenging population with significant unmet medical need.

### Objective
To determine the effect of omalizumab on clinically significant asthma exacerbations (requiring systemic corticosteroids) in the first omalizumab study to exclusively enroll patients from this difficult-to-treat patient population.

### Methods
Following a run-in phase, patients (12–75 yrs) inadequately controlled despite therapy with high-dose ICS and long-acting $\beta_2$-agonists with reduced lung function and a recent history of clinically significant exacerbations were randomized to receive omalizumab or placebo for 28 wks in a double-blind, parallel-group, multicentre study.

### Results
1. A total of 419 patients were included in the efficacy analyses.
2. The clinically significant asthma exacerbation rate (primary efficacy variable), adjusted for an observed relevant imbalance in history of clinically significant asthma exacerbations, was 0.68 with omalizumab and 0.91 with placebo (26% reduction) during the 28-wk treatment phase.
3. Without adjustment, a similar magnitude of effect was seen (19% reduction), but this did not reach statistical significance.
4. Omalizumab significantly reduced severe asthma exacerbation rate and emergency visit rate.
5. Omalizumab significantly improved asthma-related quality of life, morning peak expiratory flow and asthma symptom scores.
6. The incidence of adverse events was similar between treatment groups.

### Pharmacological Information

**1. Mechanism of action [2, 12]**
Omalizumab binds selectively to human IgE and thus inhibits the binding of IgE to the high-affinity IgE receptors (FcεRI) presented on the surfaces of mast cells and basophils. Reduction in IgE- FcεRI receptor binding decreases degranulation of cells associated with allergic response and hence the extent of release of inflammatory mediators. In addition, omalizumab causes reduction of FcεRI on basophils, in addition to prevention of IgE from binding to the low affinity Fc receptors (FcεRII).
on antigen-presenting cells.

2. Pharmacokinetics:

(i) Absorption
Omalizumab has an average absolute bioavailability of 62% (mean bioavailability ranging from 53% to 71%) following subcutaneous administration. Absorption takes place slowly into serum after subcutaneous injection [2, 12]. Peak serum omalizumab concentrations are observed after 7 to 8 days following a single subcutaneous dose. In multiple dosing of omalizumab, area under the serum concentration-time curve increases up to 6 folds of that after the first dose after 14 days of administration. Steady serum concentrations are eventually reached after 14-28 days [2, 13].

(ii) Distribution
The apparent volume of distribution for omalizumab is about 78±32mL/kg. Intravenous administration of radio-labeled ¹²⁵I-Omalizumab in cynomolgus monkeys showed no apparent distribution into any organ or tissue, with most of the drug remains in the central intravascular compartment [2, 13].

(iii) Metabolism & Elimination
Omalizumab has an average serum elimination half-life of 26 days, with average apparent clearance of 2.4 ± 1.1 mL/kg/day in asthma patients [2]. However, details regarding the pathways of metabolism and clearance of omalizumab remain incompletely understood [13]. The clearance of omalizumab appears to be consistent with the recycling of IgG1 immunoglobulins via the FcRn receptor system [2, 12]. Hence, omalizumab elimination involves degradation via the liver reticuloendothelial system and endothelial cells, and excretion via the bile. The omalizumab:IgE complexes are believed to clear via interactions with Fcγ receptors within the reticuloendothelial system.

Dosage form [2]
Omalizumab is manufactured by Genentech, Novartis under the brand name Xolair®. It is available in the form of lyophilized sterile powder contained in single-use 5-cc vials. Each vial consists of 202.5 mg Omalizumab, 145.5 mg sucrose, 2.8 mg L-histidine hydrochloride monohydrate, 1.8 mg L-histidine and 0.5 mg polysorbate 20.
Omalizumab should be reconstituted with Sterile Water for Injection (SWFI), USP before use and it is administered as a SC injection. Each vial can deliver 150 mg of Omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI, USP.

**Dosage** [2]

1. **Usual dose:**

The dosage of Omalizumab is based on the pre-treatment serum IgE concentration (IU/mL) and total body weight (kg). The SC dose of the drug for adults and adolescents aged 12 or over is shown in Table 1 and Table 2. 150 to 375 mg of Omalizumab is administered subcutaneously every 2 or 4 weeks. It should be noted that no more than 150 mg is injected for each site and doses of more than 150 mg should be divided among more than one injection site.

### Table 1. Doses (milligrams) to be administrated every 4 weeks

<table>
<thead>
<tr>
<th>Pre-treatment Serum IgE (IU/mL)</th>
<th>Body Weight (kg)</th>
<th>30-60</th>
<th>&gt; 60-70</th>
<th>&gt; 70-90</th>
<th>&gt; 90-150</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 30 – 100</td>
<td></td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>300</td>
</tr>
<tr>
<td>&gt; 100 – 200</td>
<td></td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>*</td>
</tr>
<tr>
<td>&gt; 200 – 300</td>
<td></td>
<td>300</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

* See Table 2.

### Table 2. Doses (milligrams) to be administrated every 2 weeks

<table>
<thead>
<tr>
<th>Pre-treatment Serum IgE (IU/mL)</th>
<th>Body Weight (kg)</th>
<th>30-60</th>
<th>&gt; 60-70</th>
<th>&gt; 70-90</th>
<th>&gt; 90-150</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 100 – 200</td>
<td></td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>225</td>
</tr>
<tr>
<td>&gt; 200 – 300</td>
<td></td>
<td>†</td>
<td>225</td>
<td>225</td>
<td>300</td>
</tr>
<tr>
<td>&gt; 300 – 400</td>
<td></td>
<td>225</td>
<td>225</td>
<td>300</td>
<td>§</td>
</tr>
<tr>
<td>&gt; 400 – 500</td>
<td></td>
<td>300</td>
<td>375</td>
<td>§</td>
<td></td>
</tr>
</tbody>
</table>
2. Dosage adjustment:

During treatment of Omalizumab, the total IgE levels are elevated and will remain elevated for up to one year after the discontinuation of treatment. Therefore, dose determination should be based on serum IgE levels obtained at the initial dose determination if the treatment is interrupted less than one year. Total serum IgE levels may be re-tested for dose determination only if treatment interruption lasts for over one year. Besides, doses should be adjusted for significant changes in body weight.

3. Administration precautions:

- Xolair® should be stored in refrigerator at 2- 8°C (36- 46°F).
- Do not use beyond the expiration date stamped on carton.
- Xolair® for injection should be reconstituted using SWFI, USP, only.
- Xolair is for single use only and contains no preservatives.
- Reconstituted Xolair® solution should be protected from direct sunlight and used for administration within 8 hours following reconstitution when stored in the vial at 2-8°C (36- 46°F), or within 4 hours of reconstitution when stored at room temperature.
- All of the product must be withdrawn from the vial before expelling any air or excess solution from the syringe.
- Do not use if the contents of the vial do not dissolve completely by 40 minutes or any foreign particles are present.

Adverse Reactions

Pivotal clinical trials have revealed a similar rate of common adverse reactions between the omalizumab and the placebo control group. Some of the adverse reactions associated with omalizumab at a higher rate include rash, bleeding-related adverse events, gastro-intestinal and female genitourinary events.

In general, omalizumab has a good safety profile. What is worth notice is its potential to trigger anaphylaxis and malignancy. And among all, injection site reactions occur at the highest rate (45%)
Anaphylaxis

Three patients developed anaphylaxis associated with omalizumab during clinical trials, suggesting that omalizumab may have a positive correlation with life-threatening anaphylactic reactions on rare basis [14].

The alert issued by FDA in 2/2007 consolidated such a risk. Based on a review of 48 cases from 6/2003 to 12/2005, i.e. an estimated exposure of 39500 patients, at least 0.1% of the anaphylactoid reactions could be attributed to omalizumab. Anaphylaxis could be immediate (71%) occurring within the first 2 hours or delayed (13%) taking place at about 24 hours post injection. Surprisingly, majority of cases took place after repeat administration (56%), while those that occurred after the first dose comprised only 40% of the cases. 5 patients were rechallenged with omalizumab. All developed anaphylactic reactions with symptoms (which include bronchospasm, hypotension, syncope and urticaria etc.) similar to the previous episode [6, 15].

Malignancy

In clinical trials, secondary malignancy occurred in 0.5% (20 of 4127) omalizumab exposed patients compared to 0.2% (5 of 2236) control subjects. Excluding non-melanoma skin cancer, malignancies were detected among 0.4% (16) omalizumab-exposed patients and 0.1% (2) control subjects. The duration of omalizumab exposure varied among the clinical studies and was generally less than one year. The overall pattern of malignancies within the omalizumab group is remarkable for a predominantly solid organ/epithelial cancers and only one case of a hematological/lymphatic cancer. Comparisons of malignancy rates suggest an increased rate for the omalizumab-exposed subjects [14].

Injection site reaction

Injection site reaction (bruising, erythema, warmth, burning, stinging, pruritus, urticaria, pain, induration, mass, and inflammation) was common in clinical trials among both omalizumab (45%) and control groups (43%), with the time of onset smaller than one hour for both group. It appeared that omalizumab is associated with a higher rate (16% versus 14%) of prolonged injection site reactions (>7days) [2, 15].

Other significant adverse reactions are summarized in the Table 3 [12].
Table 3. Significant adverse reactions of omalizumab.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Rate among omalizumab exposed group</th>
<th>Rate among placebo control group</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash (urticaria, dermatitis, pruritus)</td>
<td>6.5%</td>
<td>4.9%</td>
<td>Incidence increased with higher plasma level of drug</td>
</tr>
<tr>
<td>Gastrointestinal system (nausea/vomiting, diarrhea, abdominal pain, and appendicitis)</td>
<td>19%</td>
<td>17.8%</td>
<td>Incidence correlated positively with the plasma level of drug</td>
</tr>
<tr>
<td>Bleeding related adverse events (epitaxis, menorrhagia, hematoma)</td>
<td>2.5%</td>
<td>1.6%</td>
<td></td>
</tr>
<tr>
<td>Low hemoglobin level</td>
<td>14%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Genitourinary related adverse events</td>
<td>11.3%</td>
<td>10.4%</td>
<td></td>
</tr>
<tr>
<td>Antibody formation</td>
<td>0.1%</td>
<td>-</td>
<td>The antibodies remitted by 11 weeks after the termination of inhaled omalizumab therapy</td>
</tr>
<tr>
<td>Others:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthalgia</td>
<td>8%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>3%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Otalgia</td>
<td>2%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>3%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Fracture</td>
<td>2%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Arm pain</td>
<td>2%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Leg pain</td>
<td>4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Generalized pain</td>
<td>7%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Some were observed at equal rate among the 2 groups:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral infections</td>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td>16%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Upper Dosing Limit
To date, no upper dosing limit has been established for omalizumab. Yet, both single intravenous dose of up to 4000mg and a cumulative dose of 44000mg over 20 weeks have not been associated with any significant sign of toxicities [2].

Precautions [2]

The long term safety data for omalizumab is not available. General precaution should be exercised in pregnant and lactating women, elderly and children. The use of omalizumab may be associated with a higher incidence of malignancy and geohelminthic infections in high risk patient group. These findings may need to be further confirmed by larger, prospective studies.

(i) Precautions in special population groups

Use in pregnancy (Category B)
There are no adequate and well-controlled studies of omalizumab in pregnant women. Reproduction studies in cynomolgus monkeys have been done. These studies showed that subcutaneous doses up to 75 mg/kg (12-fold the maximum clinical dose) of omalizumab did not elicit maternal toxicity, embryotoxicity, or teratogenicity when administered throughout organogenesis. When administered throughout late gestation, delivery and nursing, no adverse effects on fetal or neonatal growth has been reported. Since animal reproduction studies are not always predictive of human response, and IgG molecules are known to cross the placental barrier, omalizumab should be used during pregnancy only if clearly needed.

Use in lactation
IgG is excreted in human milk and therefore it is expected that omalizumab will be present in human milk. The potential for omalizumab absorption or harm to the infant are unknown since no relevant human study has been done. General caution should be exercised when administering omalizumab to a lactating woman.

Use in children
Further evaluation on omalizumab needs to be done in the pediatric population since
there is no established data for the safety and effectiveness of omalizumab in pediatric patients below the age of 12.

**Use in elderly**

There were no apparent age-related differences observed in clinical trials with 134 patients aged 65 and over. However, the number of patients involved was not sufficient to determine whether they would respond differently from younger patients.

**Use in patients at high risk for geohelminthic infections**

Data from a patient population of 137 patients at high risk for geohelminthic infections in Brazil has shown that a patient who had an infection was anywhere from 0.88 to 4.36 times as likely to have received Omalizumab than a patient who did not have an infection. The point estimate of the odds ratio for infection was 1.96. Monitoring for geohelminthic infections is therefore needed in patients at high risk for geohelminthic infections while using omalizumab. The length of monitoring for geohelminthic infections after discontinuation of omalizumab treatment is not known.

**(ii) Other precautions**

**Effect of serum IgE suppression**

Since asthma is a chronic disease, long-term studies, especially in children, are needed to evaluate the effect of serum IgE suppression throughout development; adverse effects may become apparent only with follow-up into adulthood [16].

**Malignancy**

No long-term studies have been performed in animals to evaluate the carcinogenic potential of omalizumab. Therefore the impact of long term use of omalizumab or use in patients at higher risk for malignancy (e.g. elderly, current smokers) is not known.

**Contraindications** [12]

Previous hypersensitivity reaction to the drug per se or to hamster protein, from where the drug is derived, is a contraindication of omalizumab.
**Warnings**

Anaphylaxis is always a concern for omalizumab. Clinical trials and post-marketing reports suggest that at least 0.1% of the reported cases could be attributed to omalizumab. Patients should be educated about the signs of anaphylaxis so that they could seek medical help when this potentially fatal reaction occurs. Physicians or health facilities should also be prepared and equipped to deal with anaphylaxis.

The link between malignancy and omalizumab has not been firmly established. Yet, clinical trials demonstrate a higher rate of malignancies, especially solid / organ cancer in the omalizumab exposed group. Clinicians should be aware of the potential risk of malignancy [2].

In addition, there is no formal drug interaction studies performed with omalizumab. The concomitant use of omalizumab and allergen immunotherapy has not been evaluated [2] and thus physicians and pharmacists should be cautious about the combined use of omalizumab and other medications.

**Quality of life study and cost-effectiveness analysis**

(i) Quality of life (QOL) analysis

QOL analyses on omalizumab was very limited and one QOL analysis was identified.

**STUDY 6 [17]**

This QOL analysis of **STUDY 1 [7]**.

**Conclusion**

In patients requiring moderate-to-high doses of ICSs for severe allergic asthma, the measurably improved disease control afforded by add-on omalizumab therapy is paralleled by clinically meaningful improvements in asthma-related QOL.

| **BACKGROUND** | We have previously shown that omalizumab, a recombinant humanized monoclonal anti-IgE antibody, reduces asthma exacerbations and decreases ICS requirement in patients with severe allergic asthma who were symptomatic despite moderate-to-high doses of ICSs. |
**OBJECTIVE**  The aim of the present study was to assess the effects of omalizumab on asthma-related QOL.

**METHODS**  These analyses were part of a multicenter, 52-wk, randomized, double-blind, placebo-controlled study assessing the efficacy, safety, and tolerability of subcutaneous omalizumab (≥0.016 mg/kg of IgE [in IU/mL] per 4 wks) in 525 adults with severe allergic asthma. A 16-wk steroid-stable phase was followed by a 12-wk steroid reduction phase and a 24-wk double-blind extension phase. The effect of treatment on asthma-related QOL was evaluated by using the Asthma Quality of Life Questionnaire (AQLQ) administered at baseline and at wks 16, 28, and 52.

**RESULTS**

1. The 2 treatment groups were comparable in terms of baseline AQLQ scores. At wks 16, 28, and 52, omalizumab treated patients demonstrated statistically significant improvements across all AQLQ domains, as well as in overall score.
2. A greater proportion of patients receiving omalizumab achieved a clinically meaningful improvement in asthma-related QOL during each phase of the study. Greater than 50% of both patients and investigators rated treatment similarly with omalizumab as excellent or good compared with less than 40% of placebo recipients.

(ii) **Cost-effectiveness analysis (CEA) [18]**

This is the first CEA of omalizumab in asthma no other CEA had been identified. The study showed that omalizumab is clearly more expensive than other controller medications in patients with moderate allergic asthma (Table .4). However, it could be cost saving if it is used in a very restricted group of patients with severe asthma.

**BACKGROUND**  Omalizumab can reduce hospitalization and emergency department visits and improve quality of life in patients with moderate-to-severe, suboptimally controlled allergic asthma. Given the high cost and modest efficacy of this agent, it is not clear that it is cost-effective if given to a broad population with asthma.

**OBJECTIVE**  The purpose of this study was to evaluate the cost-effectiveness of omalizumab in adults and adolescents with moderate-to-severe allergic asthma.
METHODS  A retrospective economic analysis was performed to determine the cost-effectiveness of omalizumab using 52-wk data from 2 randomized controlled clinical trials in adults and adolescents with moderate-to-severe allergic asthma. The analysis was conducted from a third-party payer's perspective, and only direct costs were considered.

RESULTS  The incremental cost-effectiveness ratios showed that the cost to achieve an additional successfully controlled day was US $523, and the daily cost to achieve at least a 0.5-point increase in Asthma Quality of Life Questionnaire score was $378 in 2003 dollars.

CONCLUSION  From a pharmacoeconomic standpoint, omalizumab would be better used in allergic asthmatic patients with poorly controlled symptoms despite maximal therapy, given the high cost and modest efficacy of this agent. It could be cost saving if given to nonsmoking patients who are hospitalized 5 or more times or 20 days or longer per year despite maximal asthma therapy.

Table 4. Mean daily treatment costs (per person; 2003 US dollars)

<table>
<thead>
<tr>
<th></th>
<th>Cost per day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Omalizumab</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>0.04</td>
</tr>
<tr>
<td>ED visits</td>
<td>0.01</td>
</tr>
<tr>
<td>Physician office visits</td>
<td>0.03</td>
</tr>
<tr>
<td>Rescue albuterol</td>
<td>0.42</td>
</tr>
<tr>
<td>Inhaled BDP**</td>
<td>0.69</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>38.66</td>
</tr>
<tr>
<td>Total daily costs</td>
<td>39.85</td>
</tr>
</tbody>
</table>

ED: Emergence department
BDP: Beclomethasone dipropionate

However, the methodology adopted in this pharmacoeconomic study was questioned by several scholars [19, 20]. Further investigations are certainly needed to establish the cost-effectiveness of omalizumab.
**Patient Education Information** [12]

Physicians and pharmacists should provide the patients with the following information when the patients are prescribed with omalizumab in order to enhance the patient awareness of the medication and to ensure their compliances.

- **Indication**
  OMALIZUMAB (Xolair®) is an injection for treating allergic asthma that is inadequately controlled by inhaled corticosteroid. It can decrease the number of asthma attacks where the patient may experience wheezing, shortness of breath and difficulty in breathing. It may be given in combination with other agents to treat allergic asthma or allergy symptoms.

  However, the patients should be reminded that omalizumab was **NOT** used for acute management of asthma attacks. The patients should be aware of the fact that it may take time for the full effect of omalizumab to establish. So patients may not see immediate improvement in their asthma after the initiation of omalizumab therapy.

  Upon the initiation of omalizumab, the current regimen for asthma (especially oral or inhaled corticosteroids) should not be self amended unless under the direct supervision of a physician. Change in regimen should be directed by physicians only.

  In addition, generic omalizumab injection is not available.

- **Administration**
  Omalizumab injection should be administered by healthcare professionals every 2 weeks or every 4 weeks, depending on the conditions of the patients. After administration, the patient may need to stay for a short while so as to observe if any serious allergic reaction occurs (anaphylaxis).

  Blood tests are needed to determine how often omalizumab treatments are needed.

- **Side effects**
  Side effects of omalizumab may include allergic reaction such as rash and injection site reaction (warmth, burning or stinging). Some gastrointestinal disturbance may also be experienced, such as nausea/vomiting, diarrhea and abdominal pain. Some bleeding events (nosebleed or unusual bruising) and certain female genitourinary adverse events may also occur, including increase in menstruation bleed and
menstruation pain.

Rare but serious adverse effects include anaphylaxis and malignancy. The symptoms of anaphylaxis may include: hives, skin rash, itching, difficulty breathing or swallowing, or swelling of the face, throat, tongue, or lips. Patients on omalizumab should call their doctors immediately if they experience any of them.

➢ Precaution
Inform health care providers if they have lymphoma or other cancer; hypersensitivity reaction to omalizumab, other medicines, foods, dyes, or preservatives; pregnant or trying to get pregnant or lactating.
Inform health care professional for significant weight changes for dose adjustment.

References


