Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systematic review

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CRD summary
This well-conducted review concluded that the efficacy of add-on omalizumab in patients with moderate to severe allergic asthma was accompanied by an acceptable safety profile. Despite some limitations of the included studies, the authors’ conclusions and recommendations for research are appropriate.

Authors’ objectives
To determine the efficacy and safety of subcutaneous omalizumab as an add-on therapy to corticosteroids for moderate to severe persistent allergic asthma.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for full papers from 1980 to April 2010; search terms were reported. There were no language restrictions. Databases of the manufacturer and United States Food and Drug Agency were searched.

Study selection
Placebo-controlled randomised trials (RCTs) that compared subcutaneous omalizumab with placebo as an add-on to corticosteroids in patients with allergic asthma were eligible for inclusion. The primary outcomes were reduction in inhaled and/or oral corticosteroids from baseline and asthma exacerbations; various secondary outcomes were considered.

Mean age of participants ranged from 8.6 to 49 years. Mean beclomethasone was 284 to 2,750μg/day. Severity of asthma was moderate to severe. Mean baseline immunoglobulin E (IgE) was 273 IU/mL (range 179 to 470 IU/mL). Most studies administered 0.016mg/kg/IgE omalizumab every two to four weeks; drug regimen in terms of run in and stabilisation phases and duration of treatment varied considerably across studies.

Two reviewers independently selected studies for the review; disagreements were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed study quality using the five-point Cochrane risk of bias tool; disagreements were resolved by consensus.

Data extraction
Incidence of binary outcomes were extracted to enable calculation of relative risks (RR) and 95% confidence intervals (CI). For continuous outcomes, mean differences and 95% CI were extracted or calculated.

Two reviewers independently extracted data; disagreements were resolved by consensus.

Methods of synthesis
Pooled relative risks and weighted mean differences (WMD) with 95% CI were calculated using a random-effects model. Numbers needed to treat to benefit (NNTB) and harm (NNTH) were calculated. Heterogeneity was measured using the I² statistic (>60% was considered substantial). Sensitivity analyses were conducted on the primary outcome for those who experienced at least one asthma exacerbation and to investigate study quality. Subgroup analyses investigated age (<12 and ≥12 years), asthma severity (moderate/severe and severe) and duration of treatment (<24 weeks and ≥24 weeks). Publication bias was assessed using a funnel plot.

Results of the review
Eight RCTs met the inclusion criteria (3,429 participants, range 246 to 576). Six studies were in adults and adolescents (≥12 years) and two were in children (<12 years). All studies met quality assessment criteria for blinding, complete
outcome data and selective outcome reporting. Two studies met criteria for random sequence generation. One study met
criteria for allocation concealment. Only one study met all five accepted criteria.

Compared to placebo, omalizumab resulted in significantly fewer asthma exacerbations (RR 0.57, 95% CI 0.48 to 0.66,
NNTB=10, 95% CI 7 to 13; eight RCTs). There was no evidence of heterogeneity or publication bias and the result was
robust across subgroup and sensitivity analyses.

Omalizumab significantly reduced asthma exacerbations per patient (WMD -0.19, 95% CI -0.23 to -0.14; eight RCTs),
hospitalisation rates (RR 0.44, 95% CI 0.23 to 0.83; five RCTs), steroid dose (more than 50% dose reduction RR 1.34,
95% CI 1.23 to 1.46; four RCTs) and steroid use (complete withdrawal RR 1.80, 95% CI 1.42 to 2.28; four RCTs).
Some heterogeneity was observed, explained by the inclusion of children with mild asthma in one study. There was no
difference between omalizumab and placebo in the rate of withdrawal due to adverse events or serious adverse events.

Results for further secondary outcomes were reported.

**Authors' conclusions**
Data indicated that the efficacy of add-on omalizumab in patients with moderate to severe allergic asthma was
accompanied by an acceptable safety profile. The magnitude of the NNTB suggested a clinically worthwhile benefit.

**CRD commentary**
The review addressed a clear review question supported by appropriate inclusion criteria. The authors searched several
relevant sources without language restrictions. Each stage of the review was conducted in duplicate, which reduced risks
of error and bias.

Study quality was assessed using appropriate criteria and the results were reported in full and taken into account in the
analysis. The analysis was appropriate. There were some methodological limitations of the included studies
(acknowledged by the authors). All studies were funded by pharmaceutical companies.

This was a well-conducted review and the conclusions and recommendations for research are appropriate.

**Implications of the review for practice and research**

*Practice:* The authors did not report implications for practice.

*Research:* The authors stated that further studies were needed in paediatric populations and to evaluate the long-term
efficacy and safety of omalizumab.

**Funding**
None.

**Bibliographic details**
Rodrigo GJ, Neffen H, Castro-Rodriguez JA. Efficacy and safety of subcutaneous omalizumab vs placebo as add-on

**PubMedID**
20688929

**DOI**
10.1378/chest.10-1194

**Original Paper URL**
http://journal.publications.chestnet.org/content/139/1/28.abstract

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
AccessionNumber
12011001130

Date bibliographic record published
13/07/2011

Date abstract record published
14/12/2011

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.