

Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation

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Scientific summary

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Background

Allergic asthma is a long-term disorder of the airways resulting from overexpression of immunoglobulin E (IgE) in response to environmental allergens. Symptoms include wheezing, breathlessness, chest tightness and coughing. Patients with poorly controlled asthma are at high risk of exacerbations requiring additional treatment, including hospitalisations. Severe exacerbations are potentially life-threatening. British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) guidelines identify five treatment steps for both adults and children.

Omalizumab (Xolair®) is a recombinant deoxyribonucleic acid (DNA)-derived humanised monoclonal antibody indicated as add-on therapy in patients aged ≥ 6 years with severe persistent allergic asthma uncontrolled at treatment step 4 or 5. National Institute for Health and Care Excellence (NICE) guidance currently recommends use in patients aged ≥ 12 years, but not in children aged 6–11 years. This assessment was conducted as part of a NICE appraisal of omalizumab.

Objectives

To determine the clinical effectiveness, safety and cost-effectiveness of omalizumab, within its licensed indication, in addition to standard therapy, compared with standard therapy without omalizumab, for the treatment of severe persistent allergic asthma in adults and adolescents aged ≥ 12 years and children aged 6–11 years.

Methods

A systematic review of the evidence on clinical efficacy was performed. Eleven electronic databases (including MEDLINE), and additional sources were searched from inception to October 2011. The manufacturer's submission (MS) was an additional data source. Randomised controlled trials (RCTs) and observational studies addressing the review question (see *Executive summary, Objective*) were included. The primary efficacy outcome was clinically significant (CS) exacerbations. Other outcomes included asthma symptoms, unscheduled health-care use, mortality, oral corticosteroids (OCSs) use and quality of life. Because of methodological and clinical heterogeneity between trials, a narrative synthesis was applied. Adverse events of omalizumab were evaluated using data from the review of efficacy and existing reviews, regulatory agency reports and the MS. Adverse effects of OCSs were evaluated using existing systematic reviews.

A systematic review of the cost-effectiveness of omalizumab against any comparator was conducted. Two previous single technology appraisal (STA) submissions and a de novo economic evaluation submitted by the manufacturer was reviewed and critically appraised to identify key areas of uncertainty. The review findings provided the basis for development of a new decision-analytic model.

The cost-effectiveness of omalizumab was evaluated by comparing the additional costs of omalizumab add-on therapy to its additional benefits in terms of improvement in health-related quality of life (HRQoL) and reduction in exacerbations compared with standard care alone, over a lifetime horizon. Health outcomes were expressed in quality-adjusted life-years (QALYs) and costs were expressed in UK pounds sterling at a 2010 price base from the perspective of the NHS.

Cost-effectiveness estimates were presented for two base-case populations of adults and adolescents (age ≥ 12 years) and children (age 6–11 years) and subgroup populations: hospitalised for asthma in the previous year, on maintenance OCSs, or experienced three or more exacerbations in the previous year. The impact of alternative assumptions and parameter inputs was explored with scenario, one-way and probabilistic sensitivity analyses.

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Results

Number and quality of studies

Review of clinical effectiveness

Eleven RCTs were included of which three, including the INvestigation of Omalizumab seVere Asthma Trial; (INNOVATE; $n=419$) and EXALT ($n=404$), and a further subgroup [IA-04-EUP ($n=164$)], met licence criteria for adults; a single RCT subgroup met the paediatric criteria [IA-05-EUP ($n=235$)]. INNOVATE and IA-05 were double-blind and placebo-controlled, Evaluate Xolair for Asthma as Leading Treatment (EXALT) and IA-04 were open-label trials with a comparator of standard care. Five RCTs provided supportive evidence in adults, and one in children. Fifteen observational studies contributed further supportive evidence, 13 in adults and two in children.

The included RCTs were generally of high quality, but the open-label design of the EXALT and IA-04 trials placed them at high risk of bias. Observational studies had multiple sources of potential bias.

Oral corticosteroid-sparing effect of omalizumab

Evidence on the efficacy of omalizumab for OCS-sparing in adults was limited; two RCTs subgroups (one in the licensed population) and ten observational studies contributed data. There was almost no evidence in children; two small linked observational studies provided data.

Adverse effects of oral corticosteroids

A number of evidence syntheses were identified regarding the adverse events associated with OCSs; all were subject to limitations, and the reliability of the data was unclear.

Safety of omalizumab

All 11 RCTs and 12 of the observational studies identified in the clinical efficacy review reported some adverse effect data. Ten additional data sources were identified; except for one good-quality systematic review, these were not systematic.

Summary of benefits and risks

Adults and adolescents aged ≥ 12 years

Omalizumab reduced the rate of CS exacerbations including severe (CSS) exacerbations in the licensed population (INNOVATE: CS exacerbations: rate ratio: 0.74; 95% CI 0.55 to 1.00; CSS exacerbations: rate ratio 0.50; 95% CI 0.32 to 0.78; this benefit was also seen in open-label trials). Larger treatment effects were observed in omalizumab responders.

Total unscheduled health-care usage was reduced in both INNOVATE and EXALT trials (INNOVATE: rate ratio 0.56; 95% CI 0.33 to 0.97); responder populations showed reduced requirements for all types of unscheduled health care. Omalizumab statistically significantly reduced asthma symptoms, and increased asthma-related quality of life and lung capacity.

Findings from supportive trials and observational studies generally reflected those from the main RCT.

There was no randomised evidence on long-term efficacy. Evidence from observational studies, limited by small size and weak methodology, suggested sustained efficacy at periods up to 4 years.

Evidence that omalizumab treatment reduced OCS use was limited: the OCS maintenance subgroup of EXALT showed statistically significant benefits; this was not found in a subgroup of one other RCT in controlled patients. Substantive reductions in OCS use were seen in observational studies.

No adverse events associated with omalizumab not documented in the summary of product characteristics (SPC) were identified. Data on serious adverse events of special interest (anaphylaxis, malignancy and thrombotic events) were limited.

Quantitative evidence for the following known adverse events associated with OCS use was found: fracture, diabetes, peptic ulcer, cardiovascular events including myocardial infarction and stroke, cataract and glaucoma, sleep and mood disturbance, and weight gain.

Children aged <12 years

Omalizumab significantly reduced CS exacerbations in the RCT subgroup of children who met licence criteria (IA-05-EUP Rate ratio 0.662; 95% CI 0.441 to 0.995). The only health-care use benefit was reduced hospitalisations in the responder analysis. Treatment effects on symptom control and quality of life in RCTs were not statistically significant. There was no evidence on efficacy beyond 60 weeks treatment duration. There was very limited evidence of the OCS-sparing benefit of omalizumab in children; two small linked UK observational studies showed benefits. Evidence on the safety of omalizumab in children was very limited; Food and Drugs Administration (FDA) documentation did not indicate differences from adult data. There was some very limited evidence for the impact of OCSs on growth in children.

Summary of cost-effectiveness results

Summary of systematic review on existing cost-effectiveness evidence

A number of common issues and limitations were identified across the studies under consideration. These were (1) variability in the patient populations used across studies; (2) lack of consideration of additional risk factors/higher-risk subgroup populations; (3) no studies addressed the relative efficacy and safety of omalizumab and OCSs; (4) adverse effects of omalizumab or standard therapy were not considered; (5) lack of robust data for asthma-related mortality risk and HRQoL improvement with omalizumab; and (6) lack of consensus on treatment duration and persistence of treatment effect over time.

The manufacturer's de novo submission (2012)

The MS compared the costs and health outcomes of omalizumab add-on therapy with standard care alone in two separate base-case populations; one for adults and adolescents (12 years and over) and the other for children aged 6–11 years. Results were presented for the following subgroup populations: (1) adults and adolescents hospitalised for asthma in the previous year, (2) children hospitalised for asthma in the previous year, (3) adults and adolescents on maintenance OCSs. An exploratory sensitivity analysis incorporating adverse effects of maintenance use of OCSs was conducted for the maintenance OCS subgroup. The incremental cost-effectiveness ratio (ICER) ranged from £61,687 to £26,320 per QALY gained across the base-case and subgroup populations. The exploratory analysis incorporating adverse effects from maintenance OCS use reduced the ICER to £25,099 per QALY gained.

Independent assessment of cost-effectiveness

This assessment used the same model structure as the MS but a number of parameters varied, in particular the estimate of mortality. The ICER for adults and adolescents (≥ 12 years of age) is £83,822 per QALY gained, whereas the ICER for children aged 6–11 years is £78,009 per QALY gained. The results are similar for the subgroup population of three or more exacerbations in the year prior to treatment, whereas the ICER

for the other subgroup populations are lower: £46,431 for the hospitalisation subgroup in adults and adolescents, £44,142 for the hospitalisation subgroup in children and £50,181 for the maintenance OCS subgroup (adults and adolescents). The findings reflect the greater risk of exacerbations faced by more severe populations and the greater HRQoL improvement in day-to-day asthma symptoms conferred by omalizumab. The ICER for omalizumab across all populations and scenarios are above £30,000 per additional QALY gained, except for the adult and adolescent maintenance OCS subgroup population when a scenario incorporating an asthma-related mortality risk of 2.478% is used.

Discussion

Strengths, limitations of the analyses and uncertainties

There is substantial randomised evidence relating to the medium-term efficacy of omalizumab in adults in terms of exacerbations, unscheduled care, day-to-day symptoms and lung function. This is drawn from three RCTs and another subgroup in patients who meet licence criteria. Randomised data in children are limited to a single a priori but underpowered RCT subgroup which showed efficacy in reduced exacerbations and hospitalisations. There were larger benefits in omalizumab responders, who are the patients who would continue treatment beyond 16 weeks in clinical practice.

There is some evidence that omalizumab reduces requirements for OCSs in patients at step 5 treatment. This is considerably more robust data, including RCTs, in adults than in children.

Data on adverse events identified as of specific interest were limited and subject to some uncertainty.

There was a lack of RCT evidence on long-term efficacy and safety in either adults or children; only limited observational evidence was identified which suggested sustained efficacy in the adult population.

Omalizumab appears to improve health outcomes of patients but it also substantially increases the costs. The ICER estimates are more favourable in the severe subgroup population of maintenance OCSs compared with the overall population. However, the ICER remains above conventional NICE thresholds of cost-effectiveness. The key drivers of cost-effectiveness are the (1) asthma-related mortality risk; (2) HRQoL improvement associated with omalizumab; and (3) adverse effects associated with OCSs use.

Generalisability of the findings

The value of additional trial evidence was limited by lack of data on populations that met licence requirements. However, there was considerable evidence to suggest efficacy in RCTs with broader inclusion criteria. Evidence from observational studies, particularly the Asthma Patient Experience on Xolair (APEX) study, suggested that omalizumab's efficacy in RCTs and NHS clinical practice is comparable.

Conclusions

Implications for service provision

The decision problem regarding omalizumab's use in NHS clinical practice differs for patients at step 4 and step 5 treatment.

There is limited, underpowered subgroup evidence that omalizumab reduces the incidence of CS and CSS exacerbations in patients who are uncontrolled at step 5. There is limited evidence for an OCS-sparing effect of omalizumab. Evidence is even more limited in children but the documented risks for OCS use in children are high. There is no direct evidence comparing the effect of omalizumab with OCSs as add-on therapy. OCS-related adverse events represent a cost to the NHS which may persist beyond the duration of OCS treatment. Reduction of OCS use in some patients treated with omalizumab is likely to reduce both routine and emergency service use.

There is evidence that at step 4, omalizumab reduces the incidence of CS and CSS exacerbations in the short- to medium-term. There is uncertainty around the size of the treatment effect, and the long-term effects of omalizumab. The weak evidence base in children rests on a single underpowered RCT subgroup.

There is evidence of a benefit of omalizumab in other relevant outcomes: asthma symptoms, emergency care use, HRQoL and FEV₁. The evidence in children is much weaker and more uncertain. The reductions in emergency resource use represent a potential benefit to the NHS. In particular, extension of treatment to children as well as adults with severe uncontrolled allergic asthma may reduce hospitalisations in children who respond to treatment.

While omalizumab appears to improve health outcomes it also substantially increases the costs to the NHS.

For both adults and children and the subgroup populations (hospitalised in the previous year, maintenance OCSs at baseline, three or more exacerbations in the previous year), the ICERs are above conventional NICE thresholds of cost-effectiveness.

The key drivers of cost-effectiveness are the asthma-related mortality risk and, to a lower extent, the HRQoL improvement with omalizumab, and the costs and health burden associated with OCS-related adverse effects.

Suggested research priorities

1. An adequately powered double-blind placebo-controlled RCT which enrolled adults and children on maintenance OCSs with optimised treatment at baseline, with an a priori subgroup analysis of children, is warranted. This pragmatic RCT should have as few exclusion criteria as possible. It should assess OCS-sparing and clinical efficacy outcomes, including exacerbations, quality of life (assessed by EQ-5D and Asthma Quality of Life Questionnaires) and symptom control (assessed by the Asthma Control Test).
2. An individual patient data (IPD) meta-analysis of good-quality double-blind RCTs should be conducted to explore the characteristics of patients who derive greatest benefit from omalizumab treatment. This should assess exacerbations, unscheduled care, symptom reduction and quality of life.
3. Research should be undertaken to quantify the costs and health losses associated with known adverse events from long-term OCS use.
4. A registry of patients treated with omalizumab could be established. This would help to address the following needs:
 - (a) further research on quality-of-life improvement in children
 - (b) further research on day-to-day symptom reduction in both adults and children
 - (c) postmarketing surveillance and ongoing cohort studies to assess the long-term safety and efficacy of omalizumab in both adults and children
 - (d) asthma-related mortality risk and its relationship with exacerbations in patients eligible for omalizumab.

Study registration

This study was registered as PROSPERO CRD42011001625.

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