The economic value of anti-IgE in severe persistent, IgE-mediated (allergic) asthma patients: 
adaptation of INNOVATE to Sweden

Dewilde S, Turk F, Tambour M, Sandstrom T

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined standard therapy (ST) and omalizumab added to ST for the treatment of patients with severe persistent asthma. ST consisted of high-dose (2,300 microg) inhaled corticosteroids (ICS), 200 microg of long-acting beta agonists (LABA) and, in some cases, oral corticosteroids, anti-leukotrienes or theophylline.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised adult patients suffering from severe persistent allergic asthma who were uncontrolled despite Global Initiative for Asthma (GINA) Step 4 therapy (i.e. a stepwise strategy including ICS, LABA, theophylline and oral corticosteroids). The inclusion criteria were a forced expiratory volume (FEV) in 1 second of at least 40% to less than 80% of predicted normal value and continuing asthma symptoms; and at least two asthma exacerbations requiring systemic corticosteroids (or one severe exacerbation with peak expiratory flow or FEV <60% of personal best requiring systemic corticosteroids) resulting in hospital admission or emergency treatment in the past 12 months despite high-dose ICS and LABA.

Setting
The setting was primary care. The economic study was carried out in Sweden.

Dates to which data relate
The effectiveness data and most resource use data were derived from studies published between 1997 and 2005. The price year was not stated.

Source of effectiveness data
The clinical data used in the model were the exacerbation rates with ST and omalizumab plus ST (presented as relative risk), the exacerbation-related risk of fatality and death rates.

Modelling
A Markov model was constructed to simulate the clinical and economic outcomes over a lifetime time horizon. Extensive information on health states and cycle length was provided. The structure of the model showing transition across health states was provided. Assumptions on disease progression and treatment effect were also reported and justified.
Sources searched to identify primary studies
Exacerbation rates (separated into severe and non-severe) were derived from the INNOVATE study, a multi-national, randomised, placebo-controlled, double-blind trial that included patients with severe persistent allergic asthma. Data were taken from this full sample of patients and calculations were made to adapt the exacerbation rates found in the study to the model cycle length. Assumptions were made on long-term treatment effect of omalizumab plus ST (modelled constantly over 5 years). It was assumed that there would be no rebound effect at treatment discontinuation. The upper bound of exacerbation-related risk of fatality came from a Swedish study involving 240 patients. Death rates from other causes were derived from Swedish life tables.

Methods used to judge relevance and validity, and for extracting data
The primary studies appear to have been identified selectively. However, the INNOVATE trial was probably used because of its high internal validity and multi-country design, whilst the other selected studies reflected the Swedish setting.

Measure of benefits used in the economic analysis
The summary benefit measure was the quality-adjusted life-years (QALYs). These were estimated using survival data derived from life tables and utility weights obtained from two sources (the INNOVATE study and a UK study conducted at four specialty asthma centres). INNOVATE data were based on the asthma quality of life questionnaire (AQLQ), while UK data were derived from EQ-5D questionnaires. AQLQ weights were converted to the EQ-5D scores through a specially created mapping function. Life-years (LYs) without quality adjustment were also reported, but were not combined with the costs. An annual discount rate of 3% was used.

Direct costs
The analysis of the costs was performed from a societal perspective. It included the direct costs associated with ST, omalizumab, exacerbations and added years of life. A breakdown of the cost items was provided, especially for those associated with exacerbations, which included general practitioner visits, hospital visits, rehabilitation centre, emergency room visits, hospital stay and use of rescue medications. The unit costs were presented separately from the resource quantities for most items. Resource use was mainly derived from the INNOVATE study (pooled values were used). The costs were valued using prices of generic drugs for hypothetically compliant patients, average Swedish unit costs and published studies. The price year was not reported.

Statistical analysis of costs
The costs were treated deterministically in the base-case.

Indirect Costs
Productivity costs were included in the added years of life. Data on resource use and costs were taken from a published study and Swedish statistics. No details on the calculation of these costs were provided.

Currency
Euros (EUR).

Sensitivity analysis
Univariate sensitivity analyses were carried to assess the robustness of the cost-utility ratios to variations in mortality rates, discounting, utilities, exclusion of costs in added years of life, and the time horizon. A probabilistic sensitivity analysis was performed by attributing stochastic distributions to model inputs that were described for each parameter. Cost-effectiveness acceptability curves were generated, based on 5,000 simulations.
Estimated benefits used in the economic analysis
The expected lifetime QALYs were 11.595 (LYs=17.708) with ST and 12.357 (LYs=18.366) with omalizumab plus ST.

Cost results
The total costs were EUR 52,702 with ST and EUR 95,456 with omalizumab plus ST.

Synthesis of costs and benefits
The costs and QALYs were combined by calculating an incremental cost-utility ratio.

The incremental cost per QALY with omalizumab over ST was EUR 56,091 (95% confidence interval, CI: 31,328 to 120,552).

The incremental net benefit based on a threshold of EUR 53,384 was -EUR 3,356 (95% CI: -24,441 to 26,881). The negative figure indicates that there is a likelihood of omalizumab not achieving cost-effectiveness.

The univariate sensitivity analysis showed that the incremental cost per QALY ranged from EUR 39,675 with no discounting of QALYs and costs to EUR 131,130 when no asthma mortality was assumed. In general, the base-case results were strongly sensitive to variation in the risk of death due to asthma exacerbations. Reductions in the time horizon led to higher cost-utility ratios, whereas changes in other model inputs did not substantially alter the results of the analysis.

The probabilistic sensitivity analysis indicated that there is a 50% probability of cost-effectiveness at a threshold of approximately EUR 60,000.

Authors’ conclusions
Omalizumab added to standard therapy (ST) for adult patients with severe persistent asthma provided cost-offsets in terms of a reduction in exacerbation costs and improved quality of life. It also had a cost-utility ratio slightly above the usual threshold in Sweden.

CRD COMMENTARY - Selection of comparators
Given the objective of the study, the rationale for the choice of the comparators was clear and appropriate. ST was described and dosages for different medications were given. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were derived from different sources, but the bulk of the clinical data were obtained from a large clinical trial. The characteristics of the INNOVATE study make the clinical evidence used in the model robust. Other data were derived from Swedish sources. The data were not pooled as each source provided a series of estimates that were used to populate the decision model. The authors did not report any search methods or inclusion criteria. However, the choice of the INNOVATE study was justified in that it was the only randomised, clinical trial in this specific patient population. The use of Swedish data was also appropriate to the study question. An extensive sensitivity analysis on key clinical inputs was carried out.

Validity of estimate of measure of benefit
The use of QALYs as the summary benefit measure was appropriate as QALYs capture the impact of the intervention on two relevant dimensions of health (i.e. survival and quality of life) for patients with persistent asthma. QALYs have the further advantage of being comparable with the benefits of other health care interventions. Discounting was performed, as suggested in international guidelines. The approach used to evaluate the QALYs was reported and the instruments used were appropriate. The authors stated that some utility weights were elicited from a UK study, but this
appears to have been transferable to the Swedish context.

**Validity of estimate of costs**
The analysis of the costs was carried out from a broad perspective. It appears that all the relevant categories of costs have been included. There was limited information on the indirect costs. A breakdown of the direct cost items was given and the sources of the data were reported, although they were not extensively described. The price year was not reported, which limits the possibility of reflationing the total costs in other time periods. Sensitivity analyses of the costs were carried out in which the exclusion of costs associated with added years of life was tested. The costs were appropriately discounted. Resources associated with adverse events were not considered as there were no differences between the two groups of patients.

**Other issues**
The authors did not compare their findings with those from other studies. In terms of the generalisability of the study results to other settings, the authors stated that, even if the analysis focused on the Swedish context, the use of international data and the standardised treatment for patients with persistent asthma (GINA) ensures the transferability of the analysis. The results of the analysis were clearly presented and the conclusions of the analysis were consistent with the objective of the study. The authors highlighted some important assumptions of the analysis, such as the 100% patient compliance, long-term treatment effect and independence of future events from previous exacerbation rates. These appear to be very important features of the analysis and may need to be verified in future studies.

**Implications of the study**
The study results suggest that omalizumab added to ST might be a cost-effective treatment for patients with severe persistent asthma, especially in those patients at increased risk of mortality and at high-risk of requiring emergency health care during severe asthma exacerbations.

**Source of funding**
Supported by a grant from Novartis.

**Bibliographic details**
Dewilde S, Turk F, Tambour M, Sandstrom T. The economic value of anti-IgE in severe persistent, IgE-mediated (allergic) asthma patients: adaptation of INNOVATE to Sweden. Current Medical Research and Opinion 2006; 22(9): 1765-1776

**PubMedID**
16968580

**DOI**
10.1185/030079906X132389

**Other publications of related interest**
Because readers are likely to encounter and assess individual publications, NHS EED abstracts reflect the original publication as it is written, as a stand-alone paper. Where NHS EED abstractors are able to identify positively that a publication is significantly linked to or informed by other publications, these will be referenced in the text of the abstract and their bibliographic details recorded here for information.


Bousquet J, Cabrera P, Berkman N, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Antibodies, Anti-Idiotypic /economics /immunology /therapeutic use; Antibodies, Monoclonal /economics /immunology /therapeutic use; Antibodies, Monoclonal, Humanized; Asthma /economics /immunology /therapy; Double-Blind Method; Drug Costs; Female; Humans; Immunoglobulin E /immunology; Male; Markov Chains; Middle Aged; Models, Economic; Omalizumab; Placebos; Sweden

**AccessionNumber**
22006001979

**Date bibliographic record published**
31/07/2007

**Date abstract record published**
31/07/2007