Modelling the cost-effectiveness of etanercept in adults with rheumatoid arthritis in the UK

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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 use of etanercept (Enbrel), a genetically engineered protein dimmer, as a biological therapy for rheumatoid arthritis (RA) in adults who have failed to respond to at least two disease-modifying antirheumatic drugs (DMARDs).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with RA who had already failed two 6-month treatments with DMARDs, including methotrexate.

Setting
The setting was secondary care. The economic study was conducted in the UK.

Dates to which data relate
The effectiveness and resource use data were derived from studies published between 1988 and 2002. The price year was 2000.

Source of effectiveness data
The effectiveness evidence came from a review of completed studies.

Modelling
A decision tree model was constructed to estimate the costs and benefits of treatment with and without etanercept in a hypothetical cohort of 10,000 eligible patients. The model compared a sequence of etanercept monotherapy followed by traditional DMARDs versus a sequence of traditional DMARDs. Patients who failed to achieve a response to etanercept stopped treatment. The time horizon of the model was lifetime. The structure of the tree was reported in the article. The model was deterministic. A sequence of DMARDs therapies was assumed on the basis of UK cohorts of RA patients. More specifically, methotrexate was considered the first-line treatment, followed by sulphasalazine (second-line treatment), intramuscular gold (third-line treatment), leflunomide (fourth-line treatment), and cyclosporin in combination with methotrexate (fifth-line treatment).

Outcomes assessed in the review
The outcome measures assessed were:
the rate of response in the American College of Rheumatology 20 response rate (ACR 20) at 6 months;
the rate of withdrawals at each 6-month period;
the initial Health Assessment Questionnaire (HAQ) improvement;
the 6-monthly HAQ progression on treatment;
the change in utility score; and
mortality.

**Study designs and other criteria for inclusion in the review**
A formal review of the literature was not performed. The evidence on etanercept was derived from a Phase III randomised clinical trial (RCT). Results of meta-analyses, RCTs, or observational studies were used for other model inputs. Personal communications were also used.

**Sources searched to identify primary studies**
Not stated.

**Criteria used to ensure the validity of primary studies**
Not stated.

**Methods used to judge relevance and validity, and for extracting data**
Not stated.

**Number of primary studies included**
The bulk of the evidence used in the model was derived from 18 primary studies.

**Methods of combining primary studies**
Not stated.

**Investigation of differences between primary studies**
Not stated.

**Results of the review**
The rate of response in the ACR 20 at 6 months was 50% with etanercept, 37% with intramuscular gold (DMARD A), 37% with leflunomide (DMARD B) and 48% with cyclosporin (DMARD C).

The rate of withdrawals at each 6-month period was 4.04% with etanercept, 10.6% with DMARD A, 20.66% with DMARD B and 25.30% with DMARD C.

The initial HAQ improvement was -0.8421 with etanercept, -0.43 with DMARD A, -0.524 with DMARD B and -0.3531 with DMARD C.

The 6-monthly HAQ progression on treatment was 0.0075 with etanercept, and 0.017 with DMARD A, DMARD B and DMARD C.
The change in utility score was estimated directly from the change in HAQ score (formula provided).

Mortality was related to the HAQ scores. It was derived from the mortality in the general population, adjusted by a relative risk of 2.975.

Cox proportional hazard regressions were used to predict the relative risk of mortality.

Other data were reported in graphs or derived from calculations.

**Measure of benefits used in the economic analysis**
The summary benefit measure used was the quality-adjusted life-years (QALYs). These were calculated using the decision model. The QALYs were discounted at an annual rate of 1.5%.

**Direct costs**
An annual discount rate of 6% was used since lifetime costs were considered in the model. The unit costs were not presented separately from the quantities of resources used. The health services included in the economic evaluation were drugs, monitoring, and other direct health care services such as physician visits, surgical procedures and hospital admissions. The cost/resource boundary of the health care system was adopted. The drug costs were estimated from current list prices, and monitoring costs from the British Society for Rheumatology. The other costs were derived from published studies. A strong correlation between other direct health care services and the HAQ score was found based on the literature. The resource use data were mainly derived from the probability values used in the effectiveness study. All the costs were presented in 2000 values using the purchasing parity index (for costs estimated in currencies different from the one used in the current study) and the inflation adjustment.

**Statistical analysis of costs**
The costs were not treated stochastically in the base-case.

**Indirect Costs**
The indirect costs were not included in the primary economic analysis, but they were considered in the sensitivity analysis.

**Currency**
UK pounds sterling ().

**Sensitivity analysis**
Sensitivity analyses were conducted to assess the impact of including other costs in the primary analysis. For example, home help, residential and nursing home care costs on the one side, and productivity losses on the other side. Mortality rates lower than those used in the base-case were also tested in the sensitivity analyses. Other model inputs were varied in one-way sensitivity analysis.

**Estimated benefits used in the economic analysis**
The estimated discounted QALYs over a lifetime were 7.5261 with etanercept and 5.8718 with standard care.

**Cost results**
The estimated discounted total costs per patient over a lifetime were 36,213 with etanercept and 9,199 with standard care. The substantial incremental cost of etanercept over standard care was partially offset by the fact that the other direct health care costs were lower.
Synthesis of costs and benefits
An incremental analysis was performed to combine the costs and benefits. In the base-case, the incremental cost per QALY with etanercept over standard care was 16,330.

The sensitivity analysis showed that the incremental cost per QALY ranged (for the majority of parameters that were varied) from 14,000 to 21,000.

When the indirect costs were included, the cost per QALY was lower than 10,000.

The assumption that neither etanercept nor DMARDs had an effect on delaying disease progression led to an estimated cost per QALY of 42,000.

Authors' conclusions
The use of etanercept to treat patients with rheumatoid arthritis (RA) who had already failed to respond to two 6-month treatments with disease-modifying antirheumatic drugs (DMARDs) was cost-effective in comparison with standard therapy. In addition, the incremental cost per quality-adjusted life-year (QALY) was well below the accepted threshold for cost-effectiveness in the UK. This conclusion held under several scenarios considered in the analysis.

CRD COMMENTARY - Selection of comparators
The selection of the first- to fifth-line DMARD treatments was appropriate because it was discussed with clinical experts who confirmed the use of such treatments as reasonable exemplars of DMARDs in the UK. However, the authors noted that other sequences of treatment were possible. The specific sequences under evaluation were selected on the basis of available trial-based data and use in clinical practice. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The basis of the analysis of effectiveness was a synthesis of published studies. However, a review of the literature was not conducted and the methods used to identify and combine the primary studies were not reported. Only a few designs of the primary studies were described. The authors explained in detail the methods used to obtain some estimates and justified most of the estimates used in the decision model. Uncertainty was investigated in the sensitivity analysis.

Validity of estimate of measure of benefit
The use of QALYs as the summary benefit measure was appropriate to assess the impact of the intervention on the quality and length of life of patients with RA. The use of QALYs further permits comparisons with the benefits of other health care interventions. Discounting of the benefits was carried out in accordance with published guidelines.

Validity of estimate of costs
The authors reported explicitly the perspective of the study. It appears that all the relevant categories of costs have been included in the analysis. Further, secondary analyses were performed and wider perspectives were adopted, including that of society. This enhances the robustness of the economic analysis. The unit costs and the quantities of resources used were not presented separately. The sources of the cost data were reported. Resource use was based on published data and on the relationship between costs and HAQ scores. The price year was reported, which simplifies reflation exercises in other settings. The costs were treated deterministically but extensive sensitivity analyses were conducted on the cost estimates.

Other issues
The authors compared their findings with those from other published modelling studies that presented similarities, but also differences, in the methods and assumptions of the current study. In terms of the generalisability of the study
results, the costs could vary in other settings and the authors acknowledged that the study's conclusions might not be
generalisable to other countries. It was noted that the main limitation of the study related to the data available. However,
extensive sensitivity analyses were conducted, which showed the robustness of the conclusions of the study. The authors
justified their use of deterministic rather than probabilistic sensitivity analyses.

**Implications of the study**
Following the results of the current study, the National Institute for Clinical Excellence recommended the use of
etanercept in RA patients who have failed to respond to at least two DMARDs. The authors suggested that the analysis
could be re-run using more reliable data, if available in the future. The model used in the analysis could also be used to
address other issues in RA.

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None stated.

**Bibliographic details**
Brennan A, Bansback N, Reynolds A, Conway P. Modelling the cost-effectiveness of etanercept in adults with
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**Other publications of related interest**
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Crnkic M, Teleman A, Saxne T, Geborek P. Survival on drug as a tool for the evaluation of drug tolerability. Initial
experience in southern Sweden of infliximab, etanercept and leflunomide in rheumatoid arthritis (Abstract 231b).
Rheumatology 2001;40 Suppl 1:82.

**Indexing Status**
Subject indexing assigned by NLM

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