Modeling and cost-effectiveness analysis of etanercept in adults with rheumatoid arthritis in Japan: a preliminary analysis
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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 in adults with rheumatoid arthritis (RA). The initial dosage was 25 mg, administered twice-weekly as a subcutaneous injection.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of adult patients with RA who had failed first-line therapy with bucillamine.

Setting
The setting was secondary care. The economic study was carried out in Japan.

Dates to which data relate
The effectiveness data were derived from studies published between 1988 and 2004. Some resource use data were obtained from studies published between 1991 and 1996. The direct costs appear to have been expressed using 2005 values, while the indirect costs were based on 2001 prices.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies and authors' opinions.

Modelling
A Markov model with a lifetime time horizon and 6-month cycles was used to assess the clinical and economic outputs associated with the two treatment strategies. After failure to respond to bucillamine, patients entered one of two therapeutic pathways: etanercept - MTX - SSZ - MTX+SSZ or MTX - SSZ - MTX+SSZ. At the end of each cycle, patients could remain on initial therapy, switch to the next therapy if the response was inadequate, or die. Patients who did not respond to etanercept, or who experienced severe side effects, were switched to MTX monotherapy (6 mg/week). Patients who subsequently responded inadequately to MTX were switched to SSZ monotherapy (1,000 mg/day). Those who failed to respond to SSZ were switched to MTX+SSZ combination therapy. Finally, patients who did not respond to combination therapy were taken off DMARD therapy. The therapeutic path for patients in the standard care branch differed only by the exclusion of etanercept as initial therapy. A simplified structure of the model was represented graphically.
Outcomes assessed in the review
The outcomes estimated from the literature were:

the rate of response,

the 6-month discontinuation rate,

the change in Health Assessment Questionnaire (HAQ) when ACR20 was achieved,

the HAQ progression rate,

the utility values and

mortality data.

The rate of response was defined as the American College of Rheumatology criteria for 20% clinical improvement (ACR20). The HAQ was used to calculate the utility values associated with specific health states.

Study designs and other criteria for inclusion in the review
It was unclear whether a systematic review of the literature was undertaken to identify the primary studies. Data on ACR20 improvement with etanercept and other drugs were obtained from clinical trials performed in the USA. The relationship between the HAQ and health utility was derived from a survey of 309 Japanese patients with RA. Mortality data were estimated from Japanese life tables.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

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

Number of primary studies included
Eleven appear to have been used provide the primary estimates.

Methods of combining primary studies
The method used to combine the primary studies was not reported, although it would appear that the clinical data were not combined and each study provided a single value.

Investigation of differences between primary studies
Not reported.

Results of the review
The ACR20 achievement rate was 59% with etanercept, 42.3% with MTX, and 37.1% with both SSZ monotherapy and MTX+SSZ combination therapy.
The HAQ change factor when ACR20 is achieved was 0.53 with etanercept and 0.80 with MTX monotherapy.

The 6-month discontinuation rate was 2.4% with etanercept, 5.6% with MTX monotherapy, and 7.2% with both SSZ monotherapy and MTX+SSZ combination therapy.

The HAQ progression rate (HAQ units per year) was 0 with etanercept and 0.0673 with the other treatments.

The utility values were a linear function of HAQ progression. For example, the utility of a patient with HAQ equal to 1 was 0.57, while the utility of a patient with HAQ equal to 2 was 0.4. Mortality was also associated with HAQ level by an exponential function.

**Methods used to derive estimates of effectiveness**
The authors made some assumptions in the decision model.

**Estimates of effectiveness and key assumptions**
The HAQ score was assumed not to decrease in patients who did not achieve ACR20 or who discontinued therapy due to side effects.

The HAQ change factor when ACR20 was achieved was 0.71 with both SSZ monotherapy and MTX+SSZ combination therapy.

It was also implicitly assumed that the 6-month results for the percentage of patients with ACR20 improvement would be maintained over the patients’ lifetime, as would the 6-month discontinuation rate with etanercept and the other drugs.

**Measure of benefits used in the economic analysis**
The summary benefit measure used was the expected number of quality-adjusted life-years (QALYs). These were estimated by combining utility values and life expectancy in the decision model. An annual discount rate of 1.5% was applied. Details on the sources of the utility values and on the calculation approach were reported.

**Direct costs**
The analysis of the costs was carried out from a societal perspective. The direct medical costs included were for medications (including drug administration), tuberculin skin test and lung computed tomography scan (only for patients taking etanercept), the treatment of gastrointestinal side effects, and hospitalisations for RA. The unit costs were presented separately from the quantities of resources used for some items. Resource use was estimated on the basis of authors’ assumptions and data derived from studies published in 1991 and 1996. The costs came from several sources, such as medical fees, average drug prices, and medical records at an authors' institution. The costs of RA hospitalisations were linearly associated with HAQ scores. Discounting was relevant, as the costs were incurred during a long time, and an annual discount rate of 6% was applied. The direct costs seem to have been expressed using 2005 values.

**Statistical analysis of costs**
Statistical analyses of the costs were not performed.

**Indirect Costs**
The indirect costs (i.e. productivity losses due to inability to work and mortality related to RA) were included in the analysis since a societal perspective was adopted. The unit costs and the quantities of resources used were not presented separately, but the approach used to calculate the indirect costs was described. The costs were derived from employment rates and wages estimated from a labour force survey. As in the analysis of the direct costs, an annual discount rate of 6% was applied. The indirect costs were expressed using 2001 data.
Currency
Japanese yen (JPY).

Sensitivity analysis
Sensitivity analyses were performed to assess the impact of changes in some model inputs on the cost-utility ratios. The inputs varied were the cost of etanercept or DMARDs, the HAQ change factor for ACR20 responders receiving etanercept or DMARDs, the background HAQ increase rate for patients not receiving etanercept, and the ACR20 achievement rate with DMARDs or etanercept. All inputs were varied by +/- 20% of their base-case value. The results were presented using a tornado diagram.

Estimated benefits used in the economic analysis
The estimated QALYs per patient over lifetime were 6.80 with standard therapy and 9.36 with etanercept.

Cost results
The estimated costs (millions) per patient over lifetime were JPY 17.60 with standard therapy and JPY 23.99 with etanercept.

Synthesis of costs and benefits
An incremental cost-utility ratio was calculated to combine the costs and QALYs of the alternative strategies.

The incremental cost per QALY gained with etanercept over standard care was JPY 2.50 million.

The sensitivity analysis showed that the base-case cost-utility ratios were mainly sensitive to the cost of etanercept and the changes in HAQ change factor for ACR20 responders. For example, the incremental cost per QALY ranged from JPY 1.88 million to JPY 3.12 million when the cost of etanercept was varied by +/- 20%. Under no circumstances was the cost-utility ratio of etanercept above commonly used threshold values commonly used in the UK and USA (approximately JPY 5.5 million).

Authors’ conclusions
Etanercept therapy was cost-effective, in comparison with standard therapy, for adult patients with rheumatoid arthritis (RA) who have failed first-line therapy with bucillamine in Japan. This conclusion held under the different scenarios investigated in the sensitivity analysis.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear since it reflected the standard approach to the treatment of patients with RA. The dosages used were clearly reported. The authors justified the exclusion of a treatment strategy based on the combination of etanercept and a DMARD. The use of other anti-tumour necrosis factor drugs, such as infliximab or adalimamab, was not mentioned. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence was derived from selectively identified studies which do not appear to have been identified from a systematic review of the literature. The clinical data came mainly from clinical trials, which have a high internal validity. However, there was limited information on the study design and the characteristics of the patients included in the primary sources of data. The issue of homogeneity among the studies was not addressed, and the approaches used to extract and then combine the clinical estimates were not described. This would appear to be an important limitation of the study. Some assumptions were also made in the model on account of the lack of published evidence for some estimates. Of particular important was the assumption that the clinical results found in the first 6 months would last...
over the lifetime period. The sensitivity analysis did not satisfactorily address the issue of uncertainty because only a few clinical estimates were varied and these were varied over a small range.

Validity of estimate of measure of benefit
QALYs were the most appropriate benefit measure because they capture the impact of the intervention on both quality of life and survival, which are the most relevant dimensions of health for patients with RA. The instrument used to derive utility was reported, and details of the approach used to calculate the QALYs were provided. In particular, the use of Japanese patients to derive utility values represents a strength of the analysis. The use of QALYs enables comparisons with the benefits of other health care interventions. Discounting was applied.

Validity of estimate of costs
The analysis of the costs was carried out from the societal perspective, which was appropriate as productivity losses associated with RA were relevant for the patients considered in the analysis. Some unit costs were presented separately from the resource quantities. The hospital costs of RA, however, were presented as macro-categories and were related to disability scores, which is quite common in studies on RA. The cost estimates were specific to the study setting, although some variations were tested in the sensitivity analysis. Statistical analyses were not performed on the costs or resource use data. The period during which the prices were gathered was reported for the single items, but a single price year was not given. Thus, caution will be needed if attempting reflation exercises in other time periods.

Other issues
The authors compared their findings with those from other studies, and results similar to those observed in the current study were observed. The issue of the generalisability of the study results to other settings was not explicitly addressed, but some sensitivity analyses were carried out. These should improve the external validity of the study. The authors noted an important drawback of their analysis in that most epidemiological and clinical estimates were derived from studies carried out in Western countries and may not accurately reflect the Japanese setting.

Implications of the study
The study results support the use of etanercept as a valid treatment option for adults with RA in Japan, despite the high initial cost. The authors pointed out that future studies should use Japanese epidemiological and clinical estimates.

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Other publications of related interest

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