Cost-effectiveness analysis of biological treatments for rheumatoid arthritis

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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 biological monotherapies and combination therapies in the treatment of rheumatoid arthritis was studied. The therapies studied were:

- adalimumab, 40 mg every other week, with and without methotrexate (MTX; 15 mg/week);
- anakinra, 100 mg once daily, with and without MTX (15 mg/week);
- etanercept, 25 mg twice weekly, with and without MTX (15 mg/week); and
- infliximab 3 mg/kg every 8 weeks, with a loading dose (8 doses/year) plus MTX (15 mg/week).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with moderate to severe rheumatoid arthritis, who were deemed candidates for biological therapies.

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

Dates to which data relate
The effectiveness data were derived from studies published between January 1990 and January 2003. The price year was 2003.

Source of effectiveness data
The effectiveness data were derived from a review of published studies and data from the drug package inserts.

Modelling
A decision analytic model was developed using DATA 4.0 (TreeAge Software). The time horizon of the model was 1 year. Effectiveness was measured at 6 months, as it represented the usual duration of most rheumatoid arthritis trials. The patients then continued the same treatment for another 6 months, and the effectiveness was measured again at the end of that period. Where 12-month effectiveness rates were not available, 6- and 12-month effectiveness were assumed to be equivalent. The model consisted of 16 health states. In each health state patients achieved one of four
levels of response according to the American College of Rheumatology (ACR) response criteria, and also experienced one of the four levels of adverse events (e.g. none, mild, moderate, or severe) due to their treatments.

**Outcomes assessed in the review**
The outcomes assessed were:

the probabilities of achieving ACR response criteria (i.e. ACR20, ACR50 and ACR70) for patients with each treatment strategy; and

the probabilities of developing different adverse events (i.e. none, mild, moderate and severe) for patients with each treatment strategy.

**Study designs and other criteria for inclusion in the review**
Only published peer-reviewed randomised clinical trials in English were included in the review. The search was limited to articles on adalimumab, anakinra, etanercept and infliximab.

**Sources searched to identify primary studies**
The authors performed a bibliographic search of MEDLINE.

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

**Methods used to judge relevance and validity, and for extracting data**
An expert panel of rheumatologists, who had participated in the clinical trials of biological response modifiers or had experience in prescribing these new treatments to rheumatoid arthritis patients, was convened and consulted. Each expert was presented with evidence tables based on randomised clinical trials. The panel selected the relevant clinical studies on the basis of similar patient inclusion criteria and baseline characteristics.

**Number of primary studies included**
A total of 16 studies were included in the review. When published clinical studies were not available, data from the drug package inserts were used.

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

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

**Results of the review**
The probabilities of achieving ACR response criteria ACR20, ACR50 and ACR 70 were, respectively:

with adalimumab, 0.46, 0.22 and 0.12;

with anakinra, 0.43, 0.19 and 0.01;

with etanercept, 0.71, 0.40 and 0.17;
with adalimumab plus MTX, 0.672, 0.552 and 0.269;
with anakinra plus MTX, 0.42, 0.24 and 0.10;
with etanercept plus MTX, 0.82, 0.59 and 0.36; and
with infliximab plus MTX, 0.50, 0.27 and 0.08.

The probabilities of developing no, mild, moderate or severe adverse events were, respectively:
with adalimumab, 0.05, 0.84, 0.08 and 0.03;
with anakinra, 0.00, 0.90, 0.09 and 0.01;
with etanercept, 0.00, 0.86, 0.12 and 0.02;
with adalimumab plus MTX, 0.05, 0.84, 0.08 and 0.03;
with anakinra plus MTX, 0.00, 0.84, 0.14 and 0.02;
with etanercept plus MTX, 0.00, 0.95, 0.02 and 0.03; and
with infliximab plus MTX, 0.05, 0.82, 0.11 and 0.02.

Measure of benefits used in the economic analysis
The measure of benefits used was the quality-adjusted life-years (QALYs). The preference weight for each health state was measured using visual analogue scale (VAS) questions, which were obtained from a study surveying 748 patients with rheumatoid arthritis in Southern California through the mail. Of the 487 patients who returned the survey, 380 (78.8%) were females (mean age 59.4 years). The preference weights for each of the health states (i.e. no ACR, ACR20, ACR50 and ACR70) were, respectively:
0.529, 0.679, 0.800 and 0.839 for no side effects;
0.492, 0.641, 0.762 and 0.801 for mild side effects;
0.455, 0.580, 0.701 and 0.738 for moderate side effects; and
0.341, 0.408, 0.528 and 0.566 for severe side effects.

Direct costs
The direct costs of the third-party payer were included in the analysis. There were for drugs and health care resources, such as physician visits, laboratory tests and clinical care, and hospitalisations for adverse events. The drug costs were US average wholesale prices. The costs of the health care resources were derived from the 2003 American Medical Association Current Procedural Terminology codebook, the 2003 Medicare Reimbursement Fee Schedule and the Medstat Diagnosis Related Group Guide. Discounting was unnecessary, as the costs were incurred during a 1-year period, and was not performed. The study reported the mean annual costs per patient. The price year was 2003.

Statistical analysis of costs
The costs were treated as point estimates (i.e. the data were deterministic).

Indirect Costs
The indirect costs were not included.
Currency
US dollars ($).

**Sensitivity analysis**
The robustness of the model was examined by performing one-way sensitivity analyses on all model variables. Cost variables were varied from 50 to 200% of baseline, while probability variables were increased and decreased by 50% of baseline to obtain the tested ranges.

**Estimated benefits used in the economic analysis**
The QALYs obtained with each of the treatments were as follows:

- adalimumab, 0.5733;
- anakinra, 0.5733;
- etanercept, 0.6421;
- adalimumab plus MTX, 0.6608;
- anakinra plus MTX, 0.5772;
- etanercept plus MTX, 0.6919; and
- infliximab plus MTX, 0.5949.

**Cost results**
The annual costs of each of the treatments were as follows:

- adalimumab, $18,414;
- anakinra, $17,412;
- etanercept, $18,333;
- adalimumab plus MTX, $18,957;
- anakinra plus MTX, $18,045;
- etanercept plus MTX, $18,954; and
- infliximab plus MTX, $20,071.

**Synthesis of costs and benefits**
The costs and benefits were combined using an incremental cost-utility ratio (i.e. the additional cost per extra QALY gained).

Among monotherapies, when using anakinra as the reference case (due to the lowest annual costs), the incremental cost-utility ratio for etanercept was $13,387 per QALY. Etanercept dominated adalimumab, with lower costs and more QALYs gained.

Among combination therapies, when using anakinra plus MTX as the reference case (again, due to the lowest annual costs), the incremental cost-utility ratio for etanercept plus MTX was $7,925 per QALY. Etanercept plus MTX
dominated adalimumab plus MTX and infliximab plus MTX, with lower annual costs and more QALYs gained.

The results from the sensitivity analysis showed that the cost of biological response modifiers and the probabilities of achieving ACR response were the main drivers of the incremental cost-utility ratios. The costs of adverse events, probabilities for developing adverse events, health resource costs, and the cost of MTX did not affect the incremental cost-utility results.

Authors' conclusions
Anakinra was the least expensive option for monotherapy and combination therapy regimens, while etanercept dominated other treatments.

CRD COMMENTARY - Selection of comparators
The authors evaluated seven different treatment combinations for the treatment of rheumatoid arthritis. The authors reported that these were novel biological treatments. You should decide if these are widely used treatments in your own setting.

Validity of estimate of measure of effectiveness
The authors did not undertake a systematic review of the literature (only one database was searched and unpublished literature was not included). They did, however, perform a comprehensive search of MEDLINE and only included randomised controlled trials, which are considered to be the 'gold' standard study design. The authors appropriately reported the methods and conduct of the review, and used an expert panel in the treatment of rheumatoid arthritis to judge the relevance of the trials found. Further, all estimates included in the model were varied by +/- 50% in the sensitivity analysis, to test the robustness of the results to these wide changes.

Validity of estimate of measure of benefit
The estimation of benefits (QALYs) was modelled and was based on a postal survey of a reasonably large sample. The model used to derive the measure of health benefit appears to have been appropriate and was transparently reported. The use of QALYs facilitates cross-comparisons with other health care programmes that use QALYs as their benefit measure.

Validity of estimate of costs
All the categories of cost relevant to the third-party payer perspective adopted were included in the analysis. However, the authors reported that the model did not include non treatment-related adverse events and potential improvements in long-term clinical outcomes. It is unlikely though that the omission of these costs would have affected the authors' results. The costs and the quantities were not reported separately, which will limit the generalisability of the authors' results. The health care costs were derived from Medicare charges, which may not actually reflect the true cost of the intervention. Appropriate sensitivity analyses were performed on all costs, using ranges that were reasonable. Discounting was not relevant, as all the costs were incurred during a 1-year period, and was not performed. The price year was appropriately reported, which will aid any future inflation exercises.

Other issues
The authors did not compare their results with other studies comparing biological treatments with other biological treatments. However, they reported that studies comparing biological treatments with non-biological treatments found biological treatments to be cost-effective. The issue of generalisability to other settings was addressed in the sensitivity analysis. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis.

The authors reported a number of further limitations to their study. First, the trials from which effectiveness end points were derived were not based on head-to-head comparisons of these biological treatments. Second, the cost-effectiveness
was only modelled at one year. Third, since not all 1-year effectiveness end points were published, the effectiveness end points at 6 months were used and assumed to maintain the effectiveness outcomes for at least one year. Fourth, the model did not capture the fact that patients experiencing severe adverse events or lack of efficacy could discontinue treatment and switch to other treatments. Finally, the authors used a VAS as the method to elicit health state valuation, even though there is no agreement on whether this is a valid elicitation technique.

**Implications of the study**
The authors reported that a more flexible model, incorporating longer term data, may be needed to provide a more accurate estimate and enable payers, clinicians or patients to make better-informed decisions.

**Source of funding**
None stated.

**Bibliographic details**

**Other publications of related interest**


**Indexing Status**
Subject indexing assigned by CRD

**MeSH**
Antibodies, Monoclonal /therapeutic use; Arthritis, Rheumatoid /drug therapy /economics; Cost-Benefit Analysis; Decision Support Techniques; Immunoglobulin G; Methotrexate /therapeutic use; Sialoglycoproteins /therapeutic use

**AccessionNumber**
22004008222

**Date bibliographic record published**
30/09/2005

**Date abstract record published**
30/09/2005