A cost-effectiveness analysis of treatment options for patients with methotrexate-resistant 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
Six treatment options for the management of methotrexate (MTX)-resistant rheumatoid arthritis (RA) were compared: etanercept plus MTX; etanercept monotherapy; cyclosporine plus MTX; triple therapy with hydroxychloroquine, sulfasalazine and MTX; continuation of MTX monotherapy; and no second-line agent.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population was RA patients with an inadequate response to MTX. The inclusion and exclusion criteria were not reported.

Setting
It was unclear whether the setting was primary or secondary care. The model was developed in the USA.

Dates to which data relate
The efficacy data and resource use data were taken from trials published between 1995 and 1999. The price year for the unit drug costs was 1999.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of previous studies.

Modelling
A decision-analytical model, based on published models, was used to evaluate treatment options for MTX-resistant RA.

Outcomes assessed in the review
Two RA-specific measures of effectiveness were used in the model. The first was the American College of Rheumatology (ACR) 20% response criteria (ACR 20). This required improvements of at least 20% in the tender and swollen joints counts, and in 3 of 5 other core set measures: patient's global assessment, physician's global assessment, physical disability score, an acute-phase reactant value, and patient's assessment of pain.

The second measure was a weighted outcome measure of ACR responses, relative to a full weight of ACR 70 response
(ACR 70WR), derived by calculating a weighted average of the proportions of patients achieving ACR 70, ACR 50 and ACR 20 responses. The weights assigned to ACR 70, ACR 50 and ACR 20 were 1, 50/70 and 20/70, respectively.

The potential outcomes were based on the occurrence of toxicity as a side-effect, and ACR response.

Study designs and other criteria for inclusion in the review
The model used efficacy data from three double-blind, randomised controlled trials and an open trial.

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
Seven primary studies provided the effectiveness data for this model.

METHODS OF COMBINING PRIMARY STUDIES
The efficacy of each drug was reported in terms of the ACR 20 and ACR 70, which were assimilated from the results of published trials. The formula for calculating ACR 70WR was provided in the text. The authors did not state how they combined the raw ACR data from different trials.

INVESTIGATION OF DIFFERENCES BETWEEN PRIMARY STUDIES
The authors reported that the baseline characteristics of the enrolled patients in the four trials on efficacy were comparable. The authors did not report whether they investigated other differences between the studies, such as trial design.

RESULTS OF THE REVIEW
The base-case estimates for the outcomes included in the model were as follows.

Percentage efficacy of individual drug, expressed as ACR 20 relative to ACR 70WR (ACR 20/ACR 70WR):

- for MTX, 18 (range: 14 - 22)/5 (range: 4 - 6);
- for cyclosporine, 38 (range: 30 - 46)/18 (range: 14-22); and
- for etanercept, 56 (range: 45 - 57)/36 (range: 29 - 43).

Percentage probability of achieving ACR response, expressed as before (ACR 20/ACR 70WR):

- for no second-line agent, 11 (range: 9 - 13)/6 (range: 5 - 7);
- for MTX continuation, 27 (range: 22 - 32)/11 (range: 9 - 13);
- for triple therapy, 55 (range: 44 - 66)/27 (range: 22 - 32);
for cyclosporine plus MTX, 55 (range: 44 - 66)/27 (range: 22-32);
for etanercept monotherapy, 61 (range: 49 - 73)/40 (range: 32 - 48); and
for etanercept plus MTX, 68 (range: 54 - 82)/43 (range: 34 - 52).
Probability of toxicity to: no second-line agent, 0; to MTX, 0.2 (range: 0.1 - 0.3).
Proportion with major MTX toxicity, 0.1 (range: 0.02 - 0.18).
Excess probability of toxicity to: triple therapy over MTX alone, 0 (range: 0 - 0.2); cyclosporine plus MTX over MTX alone, 0 (range: 0 - 0.2); etanercept plus MTX over MTX alone, 0.
Probability of toxicity to etanercept monotherapy, 0.

**Measure of benefits used in the economic analysis**
The benefit measures used in the economic analysis were the number achieving the ACR 20 and the ACR 70WR response criteria.

**Direct costs**
The costs were estimated from data and were also derived using modelling techniques. The direct costs of each treatment option for the management of MTX-resistant RA were limited to the health care system costs of medication, monitoring, toxicity arising from therapy, and the costs of surgery that could potentially be reduced with effective treatment. The savings associated with in-patient surgical costs were estimated using an exponential formula based on the surgery-related RA costs for a particular measure of functional status (HAQ).

The quantities and costs were not analysed separately. The cost data were taken from published lists of drug and monitoring prices (1999) and published models of drug therapy for RA (1996 and 1999). The costs were not discounted due to the short timeframe of the study, which was less than 6 months. The authors did not report whether the patients were likely to use other sources of care such as social support services or informal care.

**Statistical analysis of costs**
No statistical analysis of costs was carried out.

**Indirect Costs**
Indirect costs for the price year 1999 were included in the model. These estimated the potential savings associated with improvements in RA arising from each treatment option. The indirect costs were derived by extrapolation, from a linear regression between the published HAQ scores and working capacity. The average annual wage was $24,076 in 1994, which equated to a 6-month wage of $13,421 in 1999. When multiplied by the work capacity achieved by each treatment option, this provided an estimate of the costs arising from lost productivity. The costs were not discounted due to the short timeframe of the study, i.e. 6 months.

**Currency**
US dollars ($). No conversion rate was reported.

**Sensitivity analysis**
The variability in the point estimates was explored using one-way and three-way sensitivity analyses. Details were provided of the ranges used for each cost, outcome and probability parameter in the one-way sensitivity analysis. Two three-way sensitivity analyses were conducted, varying:
the ACR 20 estimate of triple therapy outcome, cyclosporine cost reduction and different levels of cost-effectiveness threshold; and

triple therapy outcome by ACR 70WR, etanercept cost reduction and the same three levels of cost-effectiveness threshold.

**Estimated benefits used in the economic analysis**
The estimated baseline values of effectiveness, i.e. the probability of achieving ACR 20, for the management of MTX-resistant RA, over a 6-month time horizon were:

0.11 for no second-line agent;

0.27 for MTX continuation;

0.55 for triple therapy;

0.55 for cyclosporine plus MTX;

0.61 for etanercept monotherapy; and

0.68 for etanercept plus MTX.

The authors also reported a separate analysis of the effectiveness for the management of MTX-naive RA: the probabilities were 0.26 for no second-line agent and 0.46 for MTX.

**Cost results**
The estimated baseline values for the direct costs over a 6-month time horizon were:

$2,146 for no second-line agent;

$3,264 for MTX continuation;

$3,471 for triple therapy;

$4,759 for cyclosporine plus MTX;

$8,328 for etanercept monotherapy; and

$9,381 for etanercept plus MTX.

The authors also reported a separate analysis of the direct costs for the management of MTX-naive RA: these were $1,908 for no second-line agent and $2,683 for MTX.

The estimated baseline values for the total costs (including indirect costs) over a 6-month time horizon were:

$12,842 for no second-line agent;

$13,810 for MTX continuation;

$13,492 for triple therapy;

$14,780 for cyclosporine plus MTX;

$18,180 for etanercept monotherapy; and
$19,083 for etanercept plus MTX.

The authors also reported a separate analysis of the total costs for the management of MTX-naive RA: these were $12,196 for no second-line agent and $12,409 for MTX.

There was no statistical analysis of costs.

**Synthesis of costs and benefits**

The study reported incremental cost-effectiveness ratios (ICERs), for direct and total, i.e. direct plus indirect, costs. The ICERs were calculated by dividing the difference in cost, by the difference in the probability of achieving ACR 20 for each strategy, compared with the next-best nondominated strategy. Strongly dominated strategies were defined as those associated with higher costs and lower effectiveness than at least one of the alternative therapies evaluated. Weakly dominated strategies were those associated with a higher ICER than the next most expensive option.

The ICERs using direct costs were: MTX continuation, dominated (weak); triple therapy, $2,900 per ACR 20; cyclosporine plus MTX, dominated (strong); etanercept monotherapy, dominated (weak); etanercept plus MTX, $43,900 per ACR 20.

The ICERs using total costs were: MTX continuation, dominated (strong); triple therapy, $1,500 per ACR 20; cyclosporine plus MTX, dominated (strong); etanercept monotherapy, dominated (weak); etanercept plus MTX, $42,600 per ACR 20.

The study also reported ICERs for the treatment of MTX-naive RA: $4,000 per ACR 20 and $1,100 per ACR 20 for direct and total costs, respectively.

A detailed sensitivity analysis was reported in this paper, the results of which did not generally affect the results of the baseline analysis. In the sensitivity analysis of cyclosporine cost for an ACR 20 or ACR 70WR outcome, a 75% reduction in cost was needed to keep cyclosporine from being eliminated from cost-effectiveness consideration, i.e. to become nondominated. A substantial reduction in the cost of cyclosporine was necessary to render the cyclosporine-MTX combination cost-effective. At least a 70% reduction in etanercept drug cost was necessary for etanercept monotherapy to cost less in total. Alternatively, etanercept would have to be associated with a 20% higher probability of achieving an ACR 20 response to be cost-effective.

**Authors’ conclusions**

The analysis indicated that if MTX is cost-effective for MTX-naive RA in achieving ACR 20 or ACR 70WR over a 6-month period, then it is most likely that triple therapy is cost-effective for MTX-resistant RA immediately after an inadequate response to MTX therapy. The most efficacious options, etanercept plus MTX or etanercept over triple therapy, incurred much higher incremental costs per ACR 20 or ACR 70WR.

**CRD COMMENTARY - Selection of comparators**

The relevant comparators for this model were selected on the basis of recent RCTs evaluating the treatment of MTX-resistant RA. It was not reported if these options reflect current practice in the USA. Before generalising the results, the reader should consider whether these six treatment options reflect the current approach to clinical practice in their own setting.

Validity of estimate of effectiveness:

This study reported the design and implementation of a decision-analytic model built to estimate the cost-effectiveness of six treatment options for patients with MTX-resistant RA. The study was well designed in that it reported clearly the study perspective, the time horizon and definition of parameters included in the model.

The authors did not report the search strategy, or the inclusion or exclusion criteria for the studies included in the review. Furthermore, they did not report whether they reviewed the included studies for quality in terms of study...
design. Thus, the reader cannot be sure whether the point estimates used in the baseline analysis were taken from good quality published studies. Systematic searches of literature sources should have been undertaken to ensure that the selection of studies included in the review was unbiased and as comprehensive as possible.

The authors did, however, report a very detailed sensitivity analysis, which indicated that the results of the model from the baseline analysis were robust. The authors did not report any details regarding the patient population undergoing treatment represented by the model. It would have been informative to have known whether particular patient characteristics, such as age, gender and duration of RA, could have affected the response to the six treatment options under evaluation.

Validity of estimate of benefit:

The measure of benefit used in this model was taken from published clinical trials and, as such, was an efficacy measure specific to RA. Thus, it is not possible to compare the results of this study with those for other health care interventions. If a utility-based outcome measure had been used this comparison would have been possible.

Validity of estimate of costs

The direct costs included in the study were limited to medical costs. The authors did not report whether other costs of care, such as social support services or informal care, were relevant. In diseases that involve significant disability these costs may be important. In terms of generalisability, the price years were given but the resource quantities and unit costs were not. The breakdown of total costs was therefore unknown.

Other issues

Generalisability was examined through the sensitivity analysis and by comparison with the results of other studies. The authors do not appear to have presented their results selectively. Their conclusions are in line with the population considered, although details on the baseline characteristics of the sample studied should have been given. The authors acknowledged the limitations of their study, such as those relating to the validity of the effectiveness estimates and the measure of benefit.

Implications of the study

In the baseline analysis with ACR 20 or ACR 70WR, MTX continuation, cyclosporine plus MTX, and etanercept monotherapy cost more but were dominated; these options were not cost-effective. The least expensive option, triple therapy, cost 1.3 times more per patient with ACR 20 and 2.1 times more per patient with ACR 70WR than MTX therapy for MTX-naive RA. In contrast, the most efficacious option, the combination of etanercept plus MTX, cost 38 times more per patient with ACR 20 and 23 times more per ACR 70WR than MTX therapy for MTX-naive RA. Whether etanercept plus MTX is cost-effective depends on whether a decision-maker is willing to pay the extra $34,800 per ACR 70WR (or $42,600 per ACR 20) over a 6-month period.

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