A cost effectiveness analysis of treatment options for methotrexate-naive 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 five new monotherapy treatment options as second-line agents for patients with methotrexate (MTX)-naive rheumatoid arthritis (RA).

Strategy 1 was etanercept.

Strategy 2 was leflunomide.

Strategy 3 was MTX (up to 15 mg weekly).

Strategy 4 was sulfasalazine (SSZ).

Strategy 5 was no second-line agent. This was also the baseline comparator.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical patient with MTX-naive RA.

Setting
The setting was unclear. The economic analysis was carried out in Boston (MA), USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1996 and 2000. The resource data were gathered from studies published between 1995 and 1999. The price year was 1999.

Source of effectiveness data
The effectiveness data were derived from a review of published studies.

Modelling
A decision analytic model (decision tree) was created, using DATA 3.5 software, to simulate the costs and the health outcomes associated with each strategy. The time horizon was 6 months, which represents the usual duration of most clinical trials of RA.
Outcomes assessed in the review
The parameters assessed in the review and used as model inputs were the occurrence of toxicity related to each therapy (major or minor) and the probability of American College of Rheumatology (ACR) response measures. Two ACR response measures were used.

The first was the ACR 20 response criteria. This represents an improvement of at least 20% in tender and swollen joint count and of at least 20% in three of five other core set measures (patient global assessment, physician global assessment, physical disability score, acute phase reactant and patient pain assessment).

As the second measure, a weighted outcome measure of ACR responses relative to the full weight of ACR 70 response (ACR 70 weighted response, ACR 70WR) was used by calculating a weighted average of proportions achieving ACR 70, ACR 50 and ACR 20. A weight of 1 was assigned to ACR 70, a weight of 50/70 to ACR 50, and a weight of 20/70 to ACR 20.

Study designs and other criteria for inclusion in the review
Clinical trials in which the drug effect was adjusted for the placebo effect were used to assess the ACR response.

Sources searched to identify primary studies
Not reported.

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

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

Number of primary studies included
Approximately 6 studies were included in the review.

Methods of combining primary studies
The results of the individual primary studies were combined using a narrative method, and using a formula to assess the probability of achieving ACR response.

Investigation of differences between primary studies
The authors did not investigate any differences between the primary studies.

Results of the review
The efficacy of SSZ was 0.39 (ACR 20) and 0.19 (ACR 70WR).

The efficacy of MTX was 0.38 (ACR 20) and 0.21 (ACR 70WR).

The efficacy of leflunomide was 0.38 (ACR 20) and 0.21 (ACR 70WR).

The efficacy of etanercept was 0.56 (ACR 20) and 0.36 (ACR 70WR).

The probabilities of achieving ACR 20 response and ACR 70 WR given no second-line agent were, respectively, 0.27
The probabilities of achieving ACR 20 response and ACR 70 WR given SSZ were, respectively, 0.56 (ACR 20) and 0.31 (ACR 70WR).

The probabilities of achieving ACR 20 response and ACR 70 WR given MTX were, respectively, 0.55 (ACR 20) and 0.33 (ACR 70WR).

The probabilities of achieving ACR 20 response and ACR 70 WR given leflunomide were, respectively, 0.55 (ACR 20) and 0.33 (ACR 70WR).

The probabilities of achieving ACR 20 response and ACR 70 WR given etanercept were, respectively, 0.68 (ACR 20) and 0.46 (ACR 70WR).

The probability of toxicity to no second-line agent was 0.0.

The probability of toxicity to SSZ was 0.2 and the proportion with SSZ major toxicity was 0.1.

The probability of toxicity to MTX was 0.2 and the proportion with MTX major toxicity was 0.1.

The probability of toxicity to leflunomide was 0.0.

The probability of toxicity to etanercept was 0.0.

Methods used to derive estimates of effectiveness
The authors made several assumptions to estimate the outcomes. The estimates appear to have been based on the authors' opinion.

Estimates of effectiveness and key assumptions
The authors assumed that patients with minor drug toxicity have the same clinical outcomes as those experiencing no drug toxicity, whereas patients with major drug toxicity were assumed to require discontinuation of therapy and to fail to achieve ACR response. It was also assumed that toxicity probabilities for SSZ were the same as those for MTX (which may bias against SSZ).

Measure of benefits used in the economic analysis
ACR responses were used as the benefit measure in the economic analysis.

Direct costs
A societal perspective was adopted. The direct costs were for medications, monitoring therapy and toxicity arising from therapy, and surgery. The medication costs were the average wholesale prices obtained from the 1999 Red Book. The monitoring costs were based on published literature or, where unavailable, by summing the costs of each monitoring component recommended by ACR for each disease modifying antirheumatic drug, or by monitoring guidelines in the package insert of leflunomide. The cost of each laboratory monitoring component was based on the 1999 Clinical Diagnostic Laboratory Fee Schedule of Health Care Financing Administration. The cost of an ophthalmologic monitoring visit for hydroxychloroquine was based on the 1999 Resource-Based Relative Value scale physician payment system data. The quantities were derived from the literature. The toxicity costs were based on hospital charges converted to costs by applying a region-specific cost-to-charge ratio. The inpatient surgical costs were derived from the literature. An exponential relationship between the Health Assessment Questionnaire (HAQ) and inpatient surgical costs was developed.

The unit costs were reported but the quantities of resources used were not. All of the costs were adjusted to 1999 US dollars using the medical care component of the Consumer Price Index from the Bureau of Labor. The total costs were
derived using a decision analytic model. The costs were not discounted, which was appropriate since they were incurred during less than 2 years.

The authors assumed that there were no toxicity costs for leflunomide or etanercept. They also assumed that the monitoring costs for etanercept were the same as those of no second-line agent, and that the toxicity cost associated with SSZ was the same as that associated with MTX.

**Statistical analysis of costs**
No statistical analysis of the costs was performed.

**Indirect Costs**
Indirect costs were included. Lost productivity due to morbidity was assessed. The authors assumed a linear relationship between work capacity and HAQ score based on published literature. The average income for working age (18 - 64) persons for 6 months was assessed through the literature. The indirect costs were not discounted.

**Currency**
US dollars ($).

**Sensitivity analysis**
One- and three-way sensitivity analyses were performed on ranges derived from the literature. Different budgetary cost-effectiveness thresholds were analysed through the sensitivity analysis.

**Estimated benefits used in the economic analysis**
See the 'Effectiveness Results' section.

**Cost results**
MTX was the least expensive option ($10,926 for 6 months), while etanercept was the most expensive option ($16,165 for 6 months). SSZ cost $11,027 for 6 months, leflunomide cost $11,428 for 6 months, and no second-line agent cost $11,379.

**Synthesis of costs and benefits**
Both MTX and SSZ cost less and were more effective than no second-line agent. MTX was cost-saving. The incremental cost-effectiveness ratio (ICER) of SSZ compared with MTX was $11,500 per patient with ACR 20 response over a 6-month period. Using the ACR 70WR, SSZ was dominated (more costly and less effective) by MTX.

Leflunomide was dominated by MTX under base-case assumptions.

The ICER of etanercept was $41,900 per ACR 20 in comparison with SSZ, and $40,800 per ACR 70WR in comparison with MTX.

When only the direct costs were included, the least expensive non-dominated option was SSZ with an ICER of $900 per ACR 20 and $1,500 per ACR 70WR compared with no second-line agent.

The relative cost-effectiveness between MTX and SSZ was sensitive to variation in relevant variables in the sensitivity analysis (ACR 20 and ACR 70 WR response, monitoring costs, toxicity costs and indirect costs). Otherwise, the extensive sensitivity analyses did not substantially affect the base-case results.
Authors' conclusions
Methotrexate (MTX) is cost-effective for MTX-naive rheumatoid arthritis (RA) in achieving American College of Rheumatology (ACR) 20 or ACR 70WR responses over a 6-month period. Based on available data, the relative cost-effectiveness between sulfasalazine (SSZ) and MTX cannot be determined with reasonable certainty. SSZ therapy would appear to be as cost-effective as MTX in achieving ACR outcomes over a 6-month period. The most efficacious option, etanercept, incurred far higher incremental costs per ACR WR than other options analysed. Whether etanercept compared with MTX is cost-effective depends on whether more than $40,000 per ACR 20 or ACR 70WR over a 6-month period is considered acceptable.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the baseline comparator (no second-line agent) was clear. The choice of the other comparators (etanercept, leflunomide, MTX and SSZ) was justified on the basis of results from randomised controlled trials. You should decide whether they represent currently used approaches in your own setting.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been undertaken. The sources searched, the criteria used to ensure the validity of the primary studies, and the method used to judge the relevance and validity of the data were not reported. It appears that the effectiveness estimates have been combined using narrative methods. The impact of differences between the primary studies was not investigated. In addition, the authors made assumptions that biased slightly against one treatment option (SSZ). There was little commentary on the quality of the retrieved studies, making it difficult to comment on the quality of the efficacy estimates. However, the impact of differences between the primary studies and the relevance of assumptions made on the estimates were assessed through a sensitivity analysis. Given the lack of reporting of the methods of the review, it was difficult to judge whether the best available evidence had been used to populate the model.

Validity of estimate of measure of benefit
The summary benefit measure was derived directly from the effectiveness measure. Please refer to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

Validity of estimate of costs
All the categories of costs relevant to the perspective adopted (societal) appear to have been included in the analysis. The costs associated with medical admission for the diagnosis and management of RA were not included, although the authors justified their exclusion: diagnosis is almost never done and flares of RA are managed in the ambulatory setting. The price year was reported, which facilitates reflation exercises. Statistical tests were not carried out and the costs were treated deterministically. Sensitivity analyses were performed on the costs, using ranges of variation obtained from the literature. Discounting was not relevant (costs incurred during less than 2 years) and, appropriately, was not performed.

Other issues
The authors did not compare their results with those from other published studies. However, the issue of generalisability to other settings was addressed. The authors reporting that the efficacy estimates were limited by the number of randomised trials included in the review. Hence, the issue of generalisability to general RA was also questioned. The results were not reported selectively and the conclusions appear to have reflected the scope of the study. The authors highlighted some limitations of their study. These focused on the poor generalisability of the results and the absence of a generic measure of effectiveness (e.g. quality-adjusted life-years) to compare their results with those from other cost-effectiveness studies.

Implications of the study
The authors did not make any specific recommendations for policy or practice.
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