Cost effectiveness of adding leflunomide to a 5-year strategy of conventional disease-modifying antirheumatic drugs in patients with rheumatoid arthritis

Maetzel A, Strand V, Tugwell P, Wells G, Bombardier C

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
Two treatment strategies for patients with severe rheumatoid arthritis (RA) were examined. The strategies comprised a standard sequence of disease-modifying antirheumatic drugs (DMARDs) with or without leflunomide (LEF), a recently approved DMARD.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with RA severe enough to require treatment with methotrexate (MTX).

Setting
The setting was secondary care. The economic study was conducted in Canada.

Dates to which data relate
Most of the effectiveness evidence came from studies published in 1999 and 2000. No dates for resource use were reported. The price year was likely to have been 1998.

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

Modelling
A 5-year Markov model was constructed to determine the economic and clinical implications of the two strategies for treating patients with severe RA. Under the standard treatment protocol patients started with MTX. A combination of MTX and sulfasalazine (SSZ), and then triple therapy (MTX, SSZ and hydroxychloroquine, HCQ), followed this. Patients who developed toxicity, or experienced a lack of efficacy, continued with gold sodium thiomalate (GST), and finally with cyclosporin A (CSA). Under the alternative strategy, LEF was included as a new option before GST. The model had cycles lasting 6 months. After each cycle, patients could experience three types of events. They continued therapy, they stopped therapy because of a lack or reduction in efficacy, or they stopped therapy on account of adverse events.
Outcomes assessed in the review
The outcomes assessed were:

the rates of all terminations and toxicity terminations;

the rate of total adverse events,

the maximum number of adverse events per patient; and

the American College of Rheumatology 20% response criteria (ACR20 response rate), defined as patients who respond to treatment by at least 20% in 5 of 7 clinical measures.

All these inputs were estimated for MTX, MTX+SSZ, triple therapy, LEF, GST, and CSA. The utility values associated with some health states (response, no response, terminate treatment, and no treatment) were also estimated. They were elicited using two approaches, the standard gamble and the rating scale.

Study designs and other criteria for inclusion in the review
A systematic review of the literature was undertaken. Clinical trials and observational studies were included in the review. The study that provided the greatest contribution was a meta-analysis.

Sources searched to identify primary studies
MEDLINE was searched from 1966 to 1997 by combining the keywords "rheumatoid arthritis" with textwords and keywords for MTX, GST, HGQ, CSA and other DMARDs, including their symptoms. References from a literature search conducted by the RA sub-group of the Cochrane Musculoskeletal Review Group were also considered.

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 withdrawal rates were derived from 126 primary studies, including 119 from the single DMARD meta-analysis. The utility values were derived from a separate study.

Methods of combining primary studies
Combined withdrawal rates and confidence intervals were obtained using parametric regression, assuming an exponential hazard function.

Investigation of differences between primary studies
Not stated.

Results of the review
The rates of all terminations were 13.5% (+/- 2.8) with MTX, 12.5% (+/- 4) with MTX+SSZ, 3.6% (+/- 1.3) with triple therapy, 31.6% (+/- 7.3) with LEF, 26% (+/- 4.3) with GST, and 19.3% (+/- 4.4) with CSA.

The rates of toxicity terminations were 6.6% (+/- 1.3) with MTX, 7.6% (+/- 2.2) with MTX+SSZ, 0.8% (+/- 0.4) with
triple therapy, 15.9% (+/- 3.5) with LEF, 14.4% (+/- 2.8) with GST, and 9.1% (+/- 2) with CSA.

The rates of total adverse events were 18.3% with MTX, 38.4% with MTX+SSZ, 16.9% with triple therapy, 16.5% with LEF, 25.2% with GST, and 36.6% with CSA.

The maximum number of adverse events per patient was 1.7 with MTX, 1.5 with MTX+SSZ, 1.5 with triple therapy, 4.5 with LEF, 1.4 with GST, and 1.7 with CSA.

The ACR20 response rate was 64.2% (+/- 6.3) with MTX, 69.4% (+/- 8.9) with MTX+SSZ, 78% (+/- 8.2) with triple therapy, 49.8% (+/- 5.5) with LEF, 47.1% (+/- 11.7) with GST, and 33.3% (+/- 10.9) with CSA.

Using the standard gamble approach, the utility values were 0.823 (+/- 0.281) with treatment response, 0.882 (+/- 0.131) with no treatment response, 0.783 (+/- 0.258) with treatment termination, and 0.695 (+/- 0.290) with no treatment (placebo).

Using the rating scale approach, the utility values were 0.768 (+/- 0.222) with treatment response, 0.706 (+/- 0.189) with no treatment response, 0.568 (+/- 0.236) with treatment termination, and 0.463 (+/- 0.217) with no treatment (placebo).

Measure of benefits used in the economic analysis
The summary benefit measures used were the number of years in a state of ACR20 response and the quality-adjusted life-years (QALYs). These were calculated using the rating scale and standard gamble approaches. Future benefits were discounted at an annual rate of 3%.

Direct costs
A discount rate of 3% was applied since the costs were incurred during a 5-year timeframe. The unit costs were not presented separately from the quantities of resources used. The health services included in the economic evaluation were drugs, monitoring (at baseline and follow-up), and the treatment of adverse events (for termination or continuation). The cost/resource boundary of the study was that of the Canadian payer. The costs and the quantities associated with the treatment of adverse events were derived from a panel of two community and three academic rheumatologists. Adverse events were categorised into 2 classes, those severe enough to cause treatment withdrawal or not necessitating treatment withdrawal.

The drug costs came from wholesale prices of a supplier to the majority of hospital-based pharmacies in Toronto, allowing for a mark-up of 10% for patients insured under the Ontario Drug Benefit Plan. The recommended dosage was considered for each drug. The costs of physician services, procedures, and laboratory tests for the monitoring and treatment of adverse events were estimated from the Ontario Schedule of Physician and Laboratory Benefits. The hospitalisation costs were estimated from the Ontario Case Costing Project database for each adverse event. Resources used for monitoring were based on directions issued for each drug in the Canadian Compendium of Pharmaceuticals and Specialties. The price year was presumably 1998.

Statistical analysis of costs
The costs were treated deterministically in the base-case.

Indirect Costs
The indirect costs were not considered.

Currency
US dollars ($). The costs were first assessed in Canadian dollars (Can$), then converted in US dollars. A conversion factor of 1.255, corresponding to the Purchasing Power Parity for Health and Medical Care in 1998, was used.
Sensitivity analysis
One-way sensitivity analyses were conducted to assess the robustness of the estimated cost-effectiveness ratios to variations in all model inputs. Second-order sensitivity analyses, using 10,000 Monte Carlo simulations, were also conducted. Each model input was attributed a probabilistic distribution. The ranges of values were derived from the literature, or from minimum or maximum observed values.

Estimated benefits used in the economic analysis
The number of years in a state of ACR20 response over a 5-year time horizon was 2.729 without LEF and 2.823 with LEF (difference 0.094).

Using the rating scale approach, the number of QALYs over a 5-year time horizon was 3.339 without LEF and 3.362 with LEF (difference 0.023).

Using the standard gamble approach, the number of QALYs over a 5-year time horizon was 3.868 without LEF and 3.885 with LEF (difference 0.017).

Cost results
The estimated 5-year costs were $8,467 without LEF and $9,698 with LEF (difference $1,231).

Synthesis of costs and benefits
Incremental cost-effectiveness ratios were calculated to combine the costs and benefits of the strategy with LEF relative to the strategy without LEF.

The incremental cost per additional year of ACR20 response was $13,096.

The incremental cost per QALY gained (rating scale) was $54,229.

The incremental cost per QALY gained (standard gamble) was $71,988.

>From the Monte Carlo simulation, the strategy with LEF relative to a strategy without LEF was:

more costly and more efficacious in 68.1% of the cases with rating scale QALYs, and 67.2% of the cases with standard gamble QALYs;

more costly and less efficacious in 31.6% (rating scale) and 32.4% (standard gamble); and

either less costly and more efficacious, or less costly and less efficacious, in 0.3% (rating scale) and 0.4% (standard gamble) of the simulations.

Nearly 57% (rating scale) and 54% standard gamble) of the cost-effectiveness ratios fell below the threshold of $100,000 per QALY gained.

The sensitivity analysis suggested that, assuming equal withdrawal rate for MTX and LEF, the cost per QALY gained would be $31,680 (rating scale) and $68,198 (standard gamble).

The results of variations in other model inputs were not reported.

Authors’ conclusions
Adding leflunomide (LEF) to a conventional protocol for the treatment of severe rheumatoid arthritis (RA) extended the time patients benefited from disease-modifying antirheumatic drug (DMARD) therapy at a reasonable cost-effectiveness and cost-utility.
CRD COMMENTARY - Selection of comparators
The choice of the comparator was clear and appropriate since a standard treatment algorithm based on DMARDs was considered. Other recently developed therapeutic alternatives, such as anti-tumour necrosis factor alpha, were not considered as comparators because they had not been approved for use when the current evaluation was undertaken. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness was based on a systematic review of the literature, the methods and conduct of which were reported. The design of the primary studies was given and most of the evidence came from a published meta-analysis. Details of the search (i.e. source and keywords) were provided. While the method used to extract the primary estimates was not described, the methods used to combine the primary estimates were given. Differences among the primary studies were not investigated. However, uncertainty was investigated in the sensitivity analysis. The authors noted that the results of the analysis were influenced by the very positive results of two main trials on triple therapy. Although clinical information on LEF was available for a time horizon of 2 years, conservative assumptions were made to extrapolate LEF efficacy over a longer timeframe.

Validity of estimate of measure of benefit
Two summary benefit measures were used in the analysis to reflect the cost-effectiveness and cost-utility approaches applied. ACR20 response was a measure specific to the disease considered in the study and is one of the most common clinical measures used in the evaluation of RA. QALYs, which were evaluated using two alternative approaches for the estimation of utility weights, represent a more generalisable measure. This measure is easily compared with the benefits of other health care interventions. The utilities were estimated using both standard gamble and rating scale approaches. The authors acknowledged that the standard gamble method did not show important differences between continuing and terminating patients. Appropriate discounting was conducted. The choice of a 5-year time horizon was adequate to assess the impact of the interventions on patient health.

Validity of estimate of costs
The authors explicitly stated the perspective adopted. It appears that all the categories of costs relevant to this perspective have been included in the analysis. The costs associated with possible joint replacements were not included and it was unclear whether they would have been relevant or not. Information on the unit costs and the quantities of resources used was not provided separately, which reduces the possibility of replicating the study in other settings. The source of economic data was reported for each item. Most information on resource use was derived from a panel of experts. The costs were treated deterministically in the base-case, but the economic inputs were varied in the sensitivity analysis. However, the results of variations in economic inputs were not reported. The costs were presumably estimated in 1998 values, although the price year was not explicitly reported. The currency conversion was conducted using the Purchasing Power Parity for Health and Medical Care. The authors noted that the costs in real life settings could be lower than those estimated in the study.

Other issues
The authors did not compare their findings with those from other studies. They also did not explicitly address the issue of the generalisability of the study results to other settings. Sensitivity analyses were conducted, but the results were not satisfactorily reported. This adversely affected the external validity of the analysis. The study referred to patients with severe RA and this was reflected in the authors' conclusions.

Implications of the study
The authors suggested that LEF should have a place in the treatment of patients with RA. However, the estimated cost-effectiveness and cost-utility ratios were often above the conventionally accepted threshold for the cost-effectiveness of health care interventions. Future studies should be conducted to corroborate the findings of the current economic evaluation.
Source of funding
Supported by an unrestricted grant to the Toronto General Research Institute from Aventis Canada Inc.

Bibliographic details

PubMedID
12522841

DOI
10.1002/art.10793

Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-Inflammatory Agents, Non-Steroidal /economics /therapeutic use; Antirheumatic Agents /economics /therapeutic use; Arthritis, Rheumatoid /drug therapy /economics; Canada; Cost-Benefit Analysis; Decision Trees; Drug Therapy, Combination; Economics, Pharmaceutical; Health Care Costs; Humans; Isoxazoles /economics /therapeutic use; Models, Statistical; Probability

AccessionNumber
22003000113

Date bibliographic record published
31/01/2005

Date abstract record published
31/01/2005