Economic evaluation of etoricoxib versus non-selective NSAIDs in the treatment of osteoarthritis and rheumatoid arthritis patients in the UK

Moore A, Phillips C, Hunsche E, Pellissier J, Crespi S

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 etoricoxib (ETO), a cyclooxygenase (COX-2) selective inhibitor, was examined. ETO was given at a dose of 60 or 90 mg/day.

Type of intervention

Treatment.

Economic study type

Cost-effectiveness analysis and cost-utility analysis.

Study population

The study population comprised a cohort of patients with osteoarthritis or rheumatoid arthritis.

Setting

The setting was primary care. The economic study was carried out in the UK.

Dates to which data relate

The effectiveness data and most resource use data were derived from studies published between 1995 and 2003. The costs came from a database published in 2001. The price year was 2002.

Source of effectiveness data

The effectiveness evidence was derived from a synthesis of completed studies.

Modelling

A decision tree model was used to assess the expected costs and consequences of ETO, compared with different options of non-selective NSAIDs, in a hypothetical cohort of 10,000 patients. GI events, major (clinically evident gastroduodenal perforations, symptomatic gastroduodenal ulcers or upper GI bleeding) and minor (those that could lead to treatment), were calculated and entered into the model to derive the total costs associated with each approach. Patients with GI problems (associated or not associated to perforation, ulcer and/or bleeding) might be hospitalised or receive outpatient treatment. Patients hospitalised could undergo surgery. The time horizon of the model was one year. The structure of the tree was reported and was identical for each strategy under investigation.

Outcomes assessed in the review

The outcomes estimated from the literature were the probabilities of:

a minor GI adverse event (nuisance symptom related),

a perforation, ulcer and/or bleeding (PUB),

a PUB given a GI adverse event,

a suspected PUB,

a suspected PUB given a GI adverse event,

a minor GI adverse event requiring treatment, and

treatment given a minor GI adverse event.

The utility values associated with specific conditions and data needed to assess expected survival were also derived from the literature.

Study designs and other criteria for inclusion in the review

It would appear that a systematic review of the literature was not undertaken to identify the primary studies. Most of the evidence came from a meta-analysis of 10 Phase IIb/III clinical trials. These trials included 3,226 patients on ETO and 2,215 on NSAIDs, who were followed up to a maximum of 190 weeks. Approximately 70% of the patients were younger than 65 years. The utility values were estimated from a study that evaluated quality of life in 60 residents from the general population of Ontario (Canada), using rating scale and standard gamble methods. No information on the design of the other studies was provided.

Sources searched to identify primary studies

Not stated.

Criteria used to ensure the validity of primary studies

No explicit criteria to ensure the validity of the primary studies were reported. However, the use of clinical evidence from a meta-analysis of clinical trials ensures the robustness of the data.

Methods used to judge relevance and validity, and for extracting data

Not stated.

Number of primary studies included

Nine primary studies provided evidence.

Methods of combining primary studies

The majority of the primary studies had already been combined in a meta-analysis. The other studies were combined using a narrative approach.

Investigation of differences between primary studies

Not stated.

Results of the review

The probabilities of a minor GI adverse event were: ETO, 0.1472; non-selective NSAIDs, 0.1840; NSAID plus PPI, 0.1840; NSAID plus H2RA 0.1840; and NSAID plus misoprostol, 0.1840.

The probabilities of a PUB were: ETO, 0.0124; non-selective NSAIDs, 0.0294; NSAID plus PPI, 0.0176; NSAID plus H2RA, 0.0294; and NSAID plus misoprostol, 0.0176.

The probabilities of a PUB given a GI adverse event were: ETO, 0.0842; non-selective NSAIDs, 0.1598; NSAID plus PPI, 0.0959; NSAID plus H2RA, 0.1598; and NSAID plus misoprostol, 0.0959.

The probabilities of a suspected PUB were: ETO, 0.0022; non-selective NSAIDs, 0.0032; NSAID plus PPI, 0.0032; NSAID plus H2RA, 0.0032; and NSAID plus misoprostol, 0.0032.

The probabilities of a suspected PUB given a GI adverse event were: ETO, 0.0024; non-selective NSAIDs, 0.0035; NSAID plus PPI, 0.0035; NSAID plus H2RA, 0.0035; and NSAID plus misoprostol, 0.0035.

The probabilities of a minor GI adverse event requiring treatment were: ETO, 0.0537; non-selective NSAIDs, 0.0551; NSAID plus PPI, 0.0551; NSAID plus H2RA, 0.0551; and NSAID plus misoprostol, 0.0551.

The probabilities of treatment given a minor GI adverse event were: ETO, 0.3997; non-selective NSAIDs, 0.3579; NSAID plus PPI, 0.3579; NSAID plus H2RA, 0.3579; and NSAID plus misoprostol, 0.3579.

The utility values (modified from the primary study to differentiate event from death) were:

0.688 for treated arthritis,

0.608 for major GI surgery,

0.626 for inpatient treatment for a major GI problem,

0.637 for outpatient treatment for a major GI problem,

0.626 for inpatient investigation for a suspected PUB,

0.663 for outpatient investigation for a suspected major GI event,

0.673 for a minor GI problem requiring treatment,

0.688 for a minor GI problem not requiring treatment, and

0.344 for death.

Misoprostol and PPIs were equally effective in reducing the incidence of clinical NSAID-induced PUBs (40% reduction in risk). H2RAs were not efficacious in the reduction of clinical PUBs.

A conservative estimate of 3.6% was used to project the death rate resulting from a PUB.

Based on life expectancies of 21.07 and 24.68 years, respectively, for men and women aged 58 in the UK, the discounted, weighted average years of life lost for a patient who dies of GI complications at age 58 years is 20.27.

Measure of benefits used in the economic analysis

The summary benefit measures used were the quality-adjusted life-years (QALYs), the number of PUBs, the number of deaths and the discounted life-years. Expected survival was discounted at an annual rate of 1.5%. All benefit measures were estimated using the modelling approach.

Direct costs

Discounting was not relevant since the costs were incurred during a 1-year timeframe. The unit costs were presented separately from the quantities of resources used. The health services included in the economic evaluation were drugs (ETO, non-selective NSAIDs, and gastroprotective agents), general practitioner visits, outpatient gastroenterologist

consultations, investigations, inpatient days and intensive care days. The drug costs also included the dispensing fee. Other costs associated with arthritis treatment were not included because it was assumed that these costs would be comparable across the treatment groups. The cost/resource boundary of the NHS was used. Resource use was estimated from published data. The costs came mainly from a retrospective analysis of general practice databases in the UK, the literature and data from NHS trusts. The average daily cost within a drug class was obtained by summing the individual products weighted by market shares. The price year was 2002.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not considered in the economic evaluation.

Currency
UK pounds sterling ().

Sensitivity analysis
Sensitivity analyses were performed to examine the robustness of the base-case results (cost-effectiveness and cost-utility ratios) to variations in the model inputs. Univariate sensitivity analyses were carried out on most relevant clinical and economic parameters using ranges observed in the literature. A probabilistic sensitivity analysis was performed by carrying out bootstrap resampling on the decision tree for 1,000 samples of size 10,000. The analysis was also run in sub-groups of patients at different risks for major GI problems.

Estimated benefits used in the economic analysis
In a hypothetical cohort of 10,000 patients, the PUBs avoided with ETO were 170.1 with respect to non-selective NSAIDs, 52.5 with respect to NSAID plus PPI, 170.1 with respect to NSAID plus H2RA, and 52.5 with respect to NSAID plus misoprostol.

The deaths avoided with ETO were 6.1 compared with non-selective NSAIDs, 1.9 compared with NSAID plus PPI, 6.1 compared with NSAID plus H2RA, and 1.9 compared with NSAID plus misoprostol.

The discounted expected life-years saved with ETO were 123.6 with respect to non-selective NSAIDs, 38.5 with respect to NSAID plus PPI, 123.6 with respect to NSAID plus H2RA, and 38.5 with respect to NSAID plus misoprostol.

The net QALYs per 10,000 patients were 6,705 with non-selective NSAIDs, 6,769 with NSAID plus PPI, 6,705 with NSAID plus H2RA, 6,769 with NSAID plus misoprostol, and 6,802 with ETO.

Cost results
The expected total daily per patient medical cost was 0.39 with non-selective NSAIDs, 1.08 with NSAID plus PPI, 0.66 with NSAID plus H2RA, 1.01 with NSAID plus misoprostol, and 0.91 with ETO.

The threshold daily cost of NSAID (the daily NSAID drug cost above which ETO is cost-saving) was 0.79 with non-selective NSAIDs, 0.10 with NSAID plus PPI, 0.52 with NSAID plus H2RA, and 0.17 with NSAID plus misoprostol.

Synthesis of costs and benefits
An incremental analysis was performed to combine the costs and benefits of the alternative strategies.

The incremental cost per PUB avoided with ETO was 12,446 in comparison with NSAID alone, and 6,438 in comparison with NSAID plus H2RA. ETO dominated NSAID plus PPI and NSAID plus misoprostol.

The incremental cost per life-year saved with ETO was 15,388 in comparison with NSAID alone and 7,279 in comparison with NSAID plus H2RA. ETO again dominated NSAID plus PPI and NSAID plus misoprostol.

The incremental cost per QALY gained with ETO was 19,766 over NSAID alone and 9,350 over NSAID plus H2RA. ETO dominated NSAID plus PPI and NSAID plus misoprostol.

The univariate sensitivity analysis showed that the key factor in determining cost-differences between ETO and non-selective NSAIDs alone was the risk of PUBs associated with the use of non-selective NSAIDs. Other model inputs had minor impact on the total costs or cost-effectiveness estimates. In the comparison between ETO and a non-selective NSAID plus H2RA or PPI, the price of gastroprotective agents and the risk of PUBs were the most relevant factors. The results were modestly sensitive to the probability of hospitalisation and the relative risk of PUB with ETO versus non-selective NSAIDs, adjusted for the effects of H2RAs.

The probability that ETO had a cost-effectiveness ratio of less than 20,000/QALY gained compared with non-selective NSAIDs alone was 61.1%. The probability of a cost-effectiveness ratio of less than 30,000/QALY gained was 93.6%.

Interesting results came from the sub-group analysis. For patients aged 56 years or older, ETO was cost-effective (cost per QALY gained below 30,000) over non-selective NSAIDs alone. For patients younger than 56 years, ETO was cost-effective in the presence of any additional risk factor. In comparison with non-selective NSAIDs co-prescribed with PPIs or misoprostol, ETO was cost-saving for patients over the age of 50 years. When compared with non-selective NSAIDs co-prescribed with H2RAs, ETO was cost-effective for patients with no additional risk factors who were aged 53 years and older. For patients aged at least 64 years with two additional risk factors, or patients aged at least 50 years with three risk factors, ETO was cost-saving versus NSAIDs plus H2RAs.

Authors' conclusions

In patients with osteoarthritis or rheumatoid arthritis, etoricoxib (ETO) was cost-saving in comparison with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) plus proton-pump inhibitors (PPIs) or misoprostol when the costs of treatment-related gastrointestinal (GI) adverse events were taken into consideration. When compared with non-selective NSAIDs alone and non-selective NSAIDs co-prescribed with histamine H2 receptor antagonists (H2RAs), the incremental costs per quality-adjusted life-year (QALY) gained with ETO were 19,766 and 9,350, respectively, which fall within the generally accepted threshold for cost-effectiveness (<30,000 per QALY gained). Sensitivity analyses showed that the risk of a perforation, ulcer and/or bleeding (PUB) associated with non-selective NSAIDs was a key factor in determining the total daily per-patient cost-differences between ETO and non-selective NSAIDs alone. In general, the model results were robust to variations in other parameters.

CRD COMMENTARY - Selection of comparators

The authors provided a justification for the choice of the comparators, the selection of which appears to have been appropriate for the study question. ETO was not compared with other cyclooxygenase (COX-2) inhibitors because of the lack of head-to-head comparisons in the literature. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness

The effectiveness evidence came from a synthesis of completed studies. The studies appear to have been identified selectively rather than using a systematic review. One of the main sources of clinical data was a meta-analysis of 10 clinical trials, which should ensure a high internal validity. Information on the whole sample size and characteristics was provided. However, few details on the other studies were given. The issue of uncertainty was investigated by performing extensive sensitivity analyses.

Validity of estimate of measure of benefit

The summary benefit measure (QALYs) was appropriate because it considers the impact of the interventions on both quality of life and survival. Other model outputs, both specific to the interventions and more generalisable (e.g. life-years saved), were also used. Discounting was applied, as UK guidelines recommended. The utility weights were derived from a published study, and some details on the approaches used to elicit quality of life values were provided.

Validity of estimate of costs

The cost categories included were consistent with the perspective adopted in the analysis. The authors justified the exclusion of some costs. The unit costs, quantities of resources used, source of data, and price year were explicitly reported, which help replicate the analysis in other settings and reflate the result in other time periods. The costs were treated deterministically in the base-case, but stochastic distributions were assigned to the economic inputs in the sensitivity analysis, where individual parameters were also varied. The authors stated that the costs of GI events avoided were not included when calculating the costs, so as to avoid double counting when the cost-effectiveness ratios were estimated.

Other issues

The authors stated that their findings were consistent with those from other published studies. The issue of the generalisability of the study results to other settings was not explicitly addressed, although extensive sensitivity analyses were used. These enhance the external validity of the results. The authors noted that the choice of some published estimates, as well as the exclusion of the indirect costs (which were not relevant from the perspective of the NHS), biased the results in favour of non-selective NSAIDs. It was noted that the analysis did not address the impact of the comparators on lower GI events. Some limitations of the analysis were also highlighted, such as the use of population-level instead of trial-based mortality data. In addition, assumptions were used to derive the risk of GI hospitalisations.

Implications of the study

Within the limitations of the model assumptions, the study results support the use of ETO for the treatment of patients with rheumatoid arthritis or osteoarthritis. In particular, the model results suggested that the difference in drug acquisition costs between ETO and non-selective NSAIDs was partially offset by expected cost-savings due to the avoidance of GI adverse events. Thus, a change of therapy from non-selective NSAIDs to ETO could reduce the incidence of serious GI adverse events at a modest incremental cost to the NHS.

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Bibliographic details

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Other publications of related interest

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steroidal antiinflammatory drugs: Omeprazole versus Misoprostol for NSAID-induced Ulcer Management (OMNIUM) Study Group. New England Journal of Medicine 1998;338:727-34.

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