Evaluation of the cost-effectiveness of Helicobacter pylori eradication triple therapy vs. conventional therapy for ulcers in Japan
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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 histamine-2 receptor antagonist (H2RA) therapy (famotidine, 40 mg daily) and eradication triple therapy with a combination of lansoprazole (30 mg twice daily), amoxicillin (750 mg twice daily), and clarithromycin (200 mg twice daily) for the treatment of patients with gastric or duodenal ulcer. A diagnostic evaluation (such as urea breath test) was carried out before the beginning of the eradication therapy. Eradication therapy lasted 7 days for patients with gastric ulcer and 5 days for those with duodenal ulcer. Conventional therapy lasted 8 weeks for gastric ulcer patients and 6 weeks for duodenal ulcer patients.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised hypothetical patients with gastric and duodenal ulcer.

Setting
The setting was not explicitly reported. The economic study was carried out in Japan.

Dates to which data relate
The effectiveness data were derived from studies published between 1985 and 1997. No dates for resource use were reported. The price year was 2000.

Source of effectiveness data
The effectiveness evidence came from a review of published studies and the authors' assumptions.

Modelling
Two Markov models, based on cycles of 2 weeks covering a time horizon of 5 years, were constructed to evaluate the costs and clinical outcomes of eradication therapy versus conventional therapy. The two models were very similar and were constructed on the basis of Japanese guidelines and specialists' opinions. An endoscopic assessment was performed after both therapies so that the appropriate treatment could be administered, depending on the success of the therapy.

Outcomes assessed in the review
The model inputs assessed in the review were:

H. pylori prevalence;

the eradication success rate with triple therapy;

the healing rate with lansoprazole and famotidine;

the annual relapse rate after eradication success and no treatment, or after eradication failure and no treatment; and

the 6-month relapse rate after H2RA maintenance therapy.

**Study designs and other criteria for inclusion in the review**

The study designs of the primary studies were not reported. The authors conducted two reviews of the literature. The first review aimed to identify data concerning relapse rates after eradication success or failure. The second literature review searched data on healing or relapse rates with famotidine. The inclusion criteria for the first review were:

H. pylori-positive gastric and duodenal ulcers;

single, double or triple H. pylori eradication therapy;

the use of an H. pylori testing method (culture, histology, rapid urease test or urea breath test) before and after eradication therapy;

the presence or absence of H. pylori was checked at 4 weeks after H. pylori eradication therapy;

12-month follow-up with no treatment; and

endoscopic examination for ulcer relapse.

The inclusion criteria for the second review were:

gastric and duodenal ulcers;

single- or double-blind trial;

healing (famotidine, 40 mg/day) and maintenance (famotidine, 20 mg/day) therapy;

randomised trial;

endoscopic examination for ulcer relapse; and

a sample size larger than 20 for each group.

**Sources searched to identify primary studies**

MEDLINE, the Cochrane Library, and JMEDICINE databases were searched for relevant articles published from 1980 to 2000. The keywords used in the review were reported.

**Criteria used to ensure the validity of primary studies**

Not stated.

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

In extracting data from the primary studies, a conservative stance towards eradication policy was adopted in order to
avoid overestimation.

**Number of primary studies included**
The reviews included 33 primary studies.

**Methods of combining primary studies**
The data on relapse rates were pooled separately, with each rate weighted by the inverse of its variance. A constant hazard was assumed when the annual or 6-month pooled relapse rates were converted into rates at 8 or 6 weeks.

**Investigation of differences between primary studies**
Not carried out.

**Results of the review**
In the case of gastric ulcer:

- the H. pylori prevalence was 94.3%;
- the eradication success rate with triple therapy was 87.5% (95% confidence interval, CI: 79.2 - 93.4);
- the healing rate was 91.9% with lansoprazole and 80.5% with famotidine;
- the annual relapse rate was 5.5% after eradication success and no treatment, and 52.3% after eradication failure and no treatment;
- the 6-month relapse rate after H2RA maintenance therapy was 24%.

In the case of duodenal ulcer:

- the H. pylori prevalence was 98.7%;
- the eradication success rate with triple therapy was 91.1% (95% CI: 83.2 - 96.1);
- the healing rate was 96.6% with lansoprazole and 82.5% with famotidine;
- the annual relapse rate was 2.9% after eradication success and no treatment, and 78.4% after eradication failure and no treatment;
- the 6-month relapse rate after H2RA maintenance therapy was 21%.

**Methods used to derive estimates of effectiveness**
The authors made some assumptions on the basis of expert opinion and Japanese practice methods.

**Estimates of effectiveness and key assumptions**
It was assumed that:

- 95% of symptomatic patients had ulcer relapses (this was extracted from an earlier study);
- 5% of the patients who received eradication therapy dropped out due to adverse events and switched to conventional therapy; and
10% of those patients with successful H. pylori eradication were confirmed to have gastrooesophageal reflux disease by annual endoscopic assessment and received proton-pump inhibitor therapy.

**Measure of benefits used in the economic analysis**
The benefit measure used in the economic analysis was the disease-free days (DFD). These were derived from healing and maintenance periods, which were calculated using the Markov models. A 3% discount rate was applied to future benefits.

**Direct costs**
A 3% annual discount rate was used since the costs were evaluated over 5 years. The unit costs were reported, but the quantities of resources were not mentioned. The health services included in the economic analysis were endoscopy, urea breath test, eradication therapy, lansoprazole, famotidine, initial and subsequent doctor's fee, and prescription fees. The cost/resource boundary adopted in the study was that of the health service payer. Resource use was estimated on the basis of the authors' assumptions. The cost data were derived from the actual Japanese medical price list and national health insurance drug acquisition prices. The price year was 2000.

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

**Indirect Costs**
The indirect costs were not included in the economic analysis.

**Currency**
Japanese yen (Y).

**Sensitivity analysis**
One- and two-way sensitivity analyses were conducted to evaluate the robustness of the estimated cost-effectiveness ratios to variations in the success rate of eradication therapy (within the range reported in the 95% CI) and the probability of endoscopic relapse in symptomatic patients (from 75 to 95%).

**Estimated benefits used in the economic analysis**
In the gastric ulcer model, the estimated discounted DFDs were 1,454 with eradication therapy and 1,313 with conventional therapy. In the duodenal ulcer model, the estimated discounted DFDs were 1,503 with eradication therapy and 1,387 with conventional therapy.

**Cost results**
In the gastric ulcer model, the estimated discounted costs per patient were Y169,719 with eradication therapy and Y390,921 with conventional therapy.

In the duodenal ulcer model, the estimated discounted costs per patient were Y134,786 with eradication therapy and Y324,689 with conventional therapy.

The annual costs of eradication therapy were always lower than those associated with conventional therapy.

**Synthesis of costs and benefits**
An average cost-effectiveness ratio was calculated to combine the costs and benefits of the two strategies in the two
decision models. In the gastric ulcer model, the cost per DFD was ¥117 with eradication therapy and ¥298 with conventional therapy. The corresponding costs in the duodenal ulcer model were ¥90 (eradication therapy) and ¥234 (conventional therapy), respectively. However, the eradication therapy was dominant because it was associated with lower costs and higher effectiveness than the conventional therapy in both patients groups. These results were robust to the variations investigated in the sensitivity analysis.

Authors’ conclusions
From the perspective of the health service payer, eradication therapy for Helicobacter pylori (H. pylori) was more cost-effective than the conventional therapy used for patients with either gastric or duodenal ulcer in Japan. The authors estimated that the treatment of all gastric and duodenal ulcers with eradication therapy, rather than conventional therapy, would save about 320 yen in Japan over a 5-year period.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear. H2RA therapy was selected because it represented the conventional approach used in Japan before combination eradication therapy was introduced. In particular, the authors stated that famotidine was selected since it represented the most widely used agent for conventional therapy. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness analysis considered two reviews of the literature, aimed at identifying relevant studies from which probability values for the decision model could be derived. It was not clear whether the reviews were conducted in a systematic manner, but specific inclusion criteria for the primary studies were reported. The authors selected the most reliable evidence and adopted weighting schemes when pooling the data derived from the primary studies. A conservative approach was used when selecting the probability values used in the model. The authors also made some assumptions and uncertainty was investigated in sensitivity analysis. Thus, the internal validity of the analysis was high. However, the authors did not consider compliance with triple therapy and the possibility of implementing re-eradication therapy.

Validity of estimate of measure of benefit
The benefit measure used in the economic analysis was DFDs, which represent a widely used end point in the treatments of patients with duodenal or gastric ulcer. It was obtained by modelling, and appropriate discounting was performed due to the long time horizon of the analysis. The decision models were described and there was a clear diagram of the model structure. The authors stressed that their model reflected actual clinical practice in Japan, although some effectiveness data came from foreign sources. The use of DFDs makes it difficult to compare the benefits of the present study with those from other interventions funded by the health service payer.

Validity of estimate of costs
The perspective adopted in the study was stated. It appears that all the relevant categories of costs have been included in the analysis. A detailed breakdown of the costs was reported and the unit costs were mentioned. However, the quantities of resources used were not reported, as they were based on the probability rates used in the decision model. The price year was stated, thus facilitating reflation exercises in other settings. The costs were treated deterministically and no sensitivity analyses were conducted on the cost inputs. The cost estimates were derived from national sources and appear to have been specific to the study setting. The authors made some assumptions to derive resource use, such that the decision model reflected Japanese practice patterns. Discounting was relevant and was performed. It would have been interesting had the authors evaluated the impact of indirect costs on the analysis, as they are clearly relevant to the patient domain studied.

Other issues
The authors compared their findings with those from other studies published in Japan. However, they did not address
the issue of the generalisability of the study results to other settings. Only a few sensitivity analyses were conducted, thus the external validity of the analysis may be low. The study referred to patients with gastric or duodenal ulcers and this was reflected in the conclusions of the analysis. The authors calculated the average cost-effectiveness ratios, but this may not be helpful to the reader since the intervention was dominant (less costly and more effective).

**Implications of the study**
The authors strongly recommended "the eradication policy for gastric and duodenal ulcers in Japan from an economic as well as clinical viewpoint". Future studies should consider compliance with triple therapy.

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