Cost effectiveness of omeprazole and ranitidine in intermittent treatment of symptomatic gastro-oesophageal reflux disease


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 omeprazole (10 or 20 mg once daily) or ranitidine (150 mg twice daily) as initial therapy, and subsequent open maintenance treatment, following initial treatment failure in the intermittent treatment of patients with symptomatic gastro-oesophageal reflux disease (GORD) with or without erosive oesophagitis. A step-up approach, involving dose titration from omeprazole 10 mg to omeprazole 20 mg or drug switching from ranitidine to omeprazole, was used.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with symptomatic GORD with or without erosive oesophagitis.

Setting
The setting was the hospital and primary care. The economic study was carried out in 6 different countries including the UK, the Republic of Ireland, Germany, France, Italy and Spain.

Dates to which data relate
The effectiveness and resource use data related to the time period between March 1994 and March 1996. The price year was 1998 for medication and 1995 for the other cost items.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was performed prospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
It was not reported whether power calculations were used to determine the sample size. The study sample initially consisted of 704 enrolled patients, 27 of whom were excluded. The remaining 677 patients were randomly assigned to receive ranitidine 150 mg (n=229), omeprazole 10 mg (n=227) or omeprazole 20 mg (n=221). The median age in the ranitidine group was 45 (range: 21 - 75) years for men and 52 (range: 19 - 75) years for women. The median age in the
omeprazole 10 mg group was 46 (range: 18 - 74) years for men and 50 (range: 19 - 74) years for women. The median age in the omeprazole 20 mg group was 44 (range: 21 - 76) years for men and 51 (range: 21 - 75) years for women.

Study design
This was an international, multi-centre, double-blind, randomised controlled study, which was carried out in 56 centres in 6 different countries (the UK, the Republic of Ireland, Germany, France, Italy and Spain). The duration of follow-up was every 3 months for 1 year after randomisation. The discontinuation rate was 29% (197), mainly because of unwillingness to continue (n=21), adverse events (n=51) or loss to follow-up (n=58). It was reported that no differences between the study groups were found with respect to discontinuation rate and the distribution of different categories of patients related to the discontinuation rate.

Analysis of effectiveness
The principle used in the analysis of effectiveness was both intention to treat and treatment completers only. The clinical outcome measures were total time off treatment, time to failure of intermittent treatment, ranking of the outcomes from best outcome (no relapse) to worst outcome (failure of the initial treatment), and the number of symptom-free days. The effect of a group of variables on time to failure of intermittent treatment was assessed using Cox proportional hazards regression. These variables included randomised treatment, week of response to initial treatment, erosive or non-erosive GORD, gender, smoking habit, duration of GORD, age, body mass index, and Helicobacter pylori status at baseline. The study groups were found to be comparable (well-matched) in terms of the baseline characteristics.

Effectiveness results
The entire study sample had a median number of days off active treatment of 142 days. This was similar in all three study groups.

According to time to failure of intermittent treatment, 47% of the patients finished the study period relying only on the intermittent treatment strategy.

The study showed that 72% of the patients were in the state of best outcome ranks (no relapse or one (or more) relapse, but in remission) until 1 year.

The rates of patients without symptoms at week 2 were 55% (20 mg) and 40% (10 mg) in the omeprazole groups versus 26% in the ranitidine group, (p<0.001; chi-squared test). However, the long-term outcomes over 1 year were not different among the study groups (22 - 27% ultimately required maintenance treatment).

The mean number of symptom-free days was 278.9 (standard deviation, SD=92.3) per patient per year in the 20-mg omeprazole (once-daily) group, versus 277.2 (SD=87.1) in the 10-mg omeprazole (once-daily) group and 273.2 (SD=88.1) in the ranitidine group, (non significant).

Clinical conclusions
Despite the non significant differences at the end of the study period, the effectiveness results were consistent with the superiority of omeprazole 20 mg once daily over omeprazole 10 mg once daily, and of omeprazole (10 and 20 mg) over ranitidine (150 mg twice daily), found in short-term analyses (2 to 4 weeks) in this patient group, both in this study and elsewhere.

Measure of benefits used in the economic analysis
The measure of benefit used in the economic analysis was the number of symptom-free days over the 1-year follow-up period of the study.
Direct costs
The costs were not discounted, but the follow-up period was only one year. The quantities were reported separately from the costs. The cost items were reported separately. The cost analysis covered the direct costs of medication, examination (visits and endoscopies) and transportation. The direct medical costs were calculated on the basis of country-specific prices and trial-wide quantities. The other cost items were calculated on the basis of both country-specific prices and quantities. The price data were obtained from MEDTAP international Inc, or from other national and international statistical reports or publications from between 1989 and 1998. The price data referred to 1995 and 1998. The cost analysis did not cover the costs of pre-entry endoscopy, visit 1, or all protocol-driven items.

Statistical analysis of costs
Student's t test was used to calculate the 95% confidence intervals for the differences in the direct medical costs. The confidence intervals for other elements of the total costs were not calculated because of the small sample size.

Indirect Costs
The indirect costs were not discounted, but this may have been appropriate due to the 1-year follow-up period. The quantities were reported separately from the costs. The cost items were reported separately. The cost analysis covered the indirect costs of productivity loss due to visits and the number of days on sick leave because of heartburn. The indirect cost items were calculated on the basis of both country-specific prices and quantities. The price data (earnings per hour for manual workers) were obtained from national and international statistical reports or publications from 1994 to 1996. The price data referred to 1995.

Currency
UK pounds sterling (£), Irish pounds (IR), German marks (DM), French francs (Ffr), Italian lire (L) and Spanish pesetas (Pta). The exchange rates at 31 March 1995 were reported as US$1= £1.6, IR1.6, DM 1.4, Ffr 4.8, L 1,706 and Pta 127.

Sensitivity analysis
Extensive one-way sensitivity analyses were performed on the effect of using branded ranitidine instead of the generic version, different rules for how to deal with incomplete data, protocol-driven costs, and the use of trial-wide data for country-specific direct cost assessment.

Estimated benefits used in the economic analysis
The mean number of days without symptoms was 278.9 (SD=92.3) per patient per year in the 20-mg omeprazole (once-daily) group, versus 277.2 (SD=87.1) in the 10-mg omeprazole (once-daily) group and 273.2 (SD=88.1) in the ranitidine group, (non significant).

Cost results
The mean total direct costs for 1 year were:

in the UK, 292 for omeprazole 20 mg, 286 for omeprazole 10 mg, and 307 for ranitidine 150 mg;

in the Republic of Ireland, IR467 for omeprazole 20 mg, IR450 for omeprazole 10 mg, and IR474 for ranitidine 150 mg;

in Germany, DM 1,119 for omeprazole 20 mg, DM 1,097 for omeprazole 10 mg, and DM 1,042 for ranitidine 150 mg;

in France, Ffr 3,122 for omeprazole 20 mg, Ffr 2,993 for omeprazole 10 mg, and Ffr 3,235 for ranitidine 150 mg;

in Italy, L 976,427 for omeprazole 20 mg, L 960,741 for omeprazole 10 mg, and L 1,064,193 for ranitidine 150 mg;
and

in Spain, Pta 67,865 for omeprazole 20 mg, Pta 66,473 for omeprazole 10 mg, and Pta 70,818 for ranitidine 150 mg.

The mean total (direct and indirect) costs were:

in the UK, 356 for omeprazole 20 mg, 376 for omeprazole 10 mg, and 527 for ranitidine 150 mg;

in the Republic of Ireland, IR577 for omeprazole 20 mg, IR592 for omeprazole 10 mg, and IR521 for ranitidine 150 mg;

in Germany, DM 1,168 for omeprazole 20 mg, DM 1,388 for omeprazole 10 mg, and DM 1,111 for ranitidine 150 mg;

in France, Ffr 3,273 for omeprazole 20 mg, Ffr 3,236 for omeprazole 10 mg, and Ffr 3,500 for ranitidine 150 mg;

in Italy, L 1,081,337 for omeprazole 20 mg, L 1,044,697 for omeprazole 10 mg, and L 1,154,754 for ranitidine 150 mg; and

in Spain, Pta 87,557 for omeprazole 20 mg, Pta 86,528 for omeprazole 10 mg, and Pta 80,007 for ranitidine 150 mg.

**Synthesis of costs and benefits**
The costs and benefits were not combined since no significant differences were found between the study arms in terms of benefits and cost measures. The sensitivity analyses revealed that, despite the substantial effects of the changes in some of the parameters on the rating of the least costly strategy, the cost differences between the strategies still did not become statistically significant.

**Authors' conclusions**
Following a pragmatic interpretation, incorporating an intermediate step-up approach, either as dose titration from omeprazole 10 mg to omeprazole 20 mg or as drug switching from ranitidine to omeprazole, the authors concluded that "the results of this study give no support to the notion that a step-up approach will result in cost savings and thereby be cost-effective".

**CRD COMMENTARY - Selection of comparators**
No specific health technologies were regarded as the comparators. You should consider if these alternatives are applicable to your own setting.

**Validity of estimate of measure of effectiveness**
The internal validity of the effectiveness results is likely to be high due to the randomised design adopted and the multinational aspects of the study. While it is unclear whether the sample was determined through power calculations, the numbers in each arm of the trial were high. Also, double-blinding was achieved and thus many of the potential biases in the trial were eliminated. The analysis was handled credibly and sensitivity analyses were conducted on important variations around effectiveness. The authors also undertook various analyses to address the potential bias caused by the patients lost to follow-up.

Validity of estimate of benefit:

The choice of symptom-free days as the principal benefit measure seems to have been appropriate for the study question. No synthesis of the costs and benefits was performed because this measure was similar between the treatment groups.

**Validity of estimate of costs**
The quantities were reported separately from the costs. Adequate details of the methods of cost estimation were given. However, the cost results (especially non-medical direct costs and indirect costs) may not be generalisable from one country to the other, as acknowledged by the authors. The authors provide a useful discussion about multi-national trial cost data. The study applied, in the base-case, trial-wide data on quantities of medication, visits and endoscopies to all countries, whilst sick leave and mode/time for transport were allowed to vary between the countries. A sensitivity analysis was conducted on the direct medical costs using country-specific data. This led to substantial changes in some countries in terms of the relative costs of omeprazole and ranitidine. The authors acknowledge the need for caution when analysing economic data from a multinational study. A useful appraisal of the impact of study period in relation to health economic analysis is given. The authors suggest 150 days would be sufficient rather than one year, as variance increases with time, making larger sample sizes necessary for economic analyses. The non significant cost (and effectiveness) results in the present study hinder incremental cost-effectiveness analyses.

**Other issues**
The authors’ conclusion seems justified. The issue of generalisability was addressed by performing sensitivity analysis. Appropriate comparisons were made with other studies.

**Implications of the study**
The study illustrates the problem of determining optimal length for a clinical study that is to serve as a basis for a health economic analysis. The 1-year period chosen for this study may, in fact, have been unnecessarily long.

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