Cost-utility of initial medical management for Crohn's disease perianal fistulae
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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
Four treatment regimens for the medical management of symptomatic perianal fistula in Crohn's disease were compared. Intervention I was 3 infliximab infusions plus 6-mercaptopurine and metronidazole as second line therapy. Intervention II was infliximab with episodic reinfusion. Intervention III was 6-mercaptopurine and metronidazole plus infliximab as second line therapy. The comparator was 6-mercaptopurine and metronidazole.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised adult patients with Crohn's disease and symptomatic perianal fistulae.

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
Effectiveness data were taken from literature published between 1979 and 2000. Cost data were taken from an administrative database containing information collected between 1 July 1993 and 31 December 1999. The price year used was 1999.

Source of effectiveness data
The source of effectiveness data was a review of previously completed studies.

Modelling
A Markov model was used to simulate a 1-year treatment period. The authors reported that the Markov cycle length was one month. The health states included in the model (initial fistula, persistent fistula, improved fistula, abscess, death and side effects from 6-mercaptopurine and metronidazole, pancreatitis and paresthesias) were defined from a literature review and consultation with gastroenterologists and colorectal surgeons. Two of the authors who were also gastroenterologists reviewed the model to check its clinical validity.

Outcomes assessed in the review
The following monthly transition probabilities were used as inputs to the model: fistula improves after infliximab; fistula recurs after infliximab; abscess occurs after infliximab; abscess recurs after incision and drainage; fistula
improves after 6-mercaptopurine and metronidazole; fistula recurs after 6-mercaptopurine and metronidazole is stopped; fistula recurs while taking 6-mercaptopurine and metronidazole; pancreatitis occurs and paresthesias occurs.

Study designs and other criteria for inclusion in the review
The authors reported that randomised controlled trials, uncontrolled experimental designs, prospective or retrospective cohort studies, case-control studies, or case series were eligible for inclusion in the review. The authors reported the following inclusion criteria: studies must have been conducted between January 1966 and April 2000; if multiple studies described the same population, the report with the strongest design and or the largest sample size was included; if one study was a follow-up to a previously published report, the data were pooled into a single estimate of effect; sample populations must have been representative of the target population; sample sizes of less than 10 patients were excluded from the review.

Sources searched to identify primary studies
The authors did not report the sources searched to identify primary studies. They did report that the initial search identified 248 citations, of which 43 were kept for further review based on the title and abstract. An additional 55 citations were identified through a review of reference lists published in the studies.

Criteria used to ensure the validity of primary studies
The criteria used to ensure the validity of primary studies were not reported.

Methods used to judge relevance and validity, and for extracting data
The authors reported that each study was systematically reviewed to assess the validity of the study design, relevance to the analysis and whether or not the study met the pre-defined inclusion criteria. A standardised data abstraction form was used. The number of reviewers involved in this process was not reported.

Number of primary studies included
Twelve primary studies were included in the analysis.

Methods of combining primary studies
The data from multiple studies were pooled using a fixed effects method to derive individual probability estimates for the model. The authors reported that each probability was converted to a constant annual rate, and solved for the monthly transition probability. The method used for the conversion was not reported. Normal distribution or exact binomial confidence limit tables were used to estimate 95% confidence intervals, depending on the sample size.

Investigation of differences between primary studies
The authors did not state if the differences between primary studies were investigated.

Results of the review
The following pooled monthly transition probabilities were used as inputs to the model.

Fistula improves after infliximab = 0.70 (95% CI: 0.63 - 0.77).
Fistula recurs after infliximab = 0.18 (95% CI: 0.10 - 0.26).
Abscess occurs after infliximab = 0.06 (95% CI = 0.01 - 0.21).
Abscess recurs after incision and drainage = 0.03 (95% CI: 0.01 - 0.08).
Fistula improves after 6-mercaptopurine and metronidazole = 0.48 (95% CI: 0.27 - 0.69).

Fistula recurs after 6-mercaptopurine and metronidazole is stopped = 0.14 (95% CI: 0.05 - 0.33).

Fistula recurs while taking 6-mercaptopurine and metronidazole = 0.01 (95% CI: 0.00 - 0.10).

Pancreatitis occurs = 0.03 (95% CI: 0.01 - 0.08).

Paresthesias occurs = 0.10 (95% CI: 0.04 - 0.16).

**Methods used to derive estimates of effectiveness**
The expert opinion of gastroenterologists and colorectal surgeons, supported by a literature review, was used to develop the structure of the model.

**Estimates of effectiveness and key assumptions**
The authors reported that clinically relevant endpoints are a subject of debate. The assumed endpoint in this analysis was ‘fistula improvement’ defined as complete closure or symptomatic improvement.

In the comparator strategy, patients who did not respond to treatment during the 12 month time-horizon were transitioned to persistent fistula and remained there until the model was complete.

The authors reported that the probability of improvement after episodic reinfusion with infliximab is unknown. For the base case for intervention II it was assumed that, for patients who responded to initial infusion, the mean probability of improvement after episodic reinfusion was equivalent to the mean probability of improvement after initial infusion.

For intervention III, the base case assumed that infliximab was equally effective for first-line and second-line infliximab therapy.

The authors reported there were no long term data on the rate of relapse after treatment with infliximab and the literature review indicated that 75% of patients lost their initial response within the first 3.75 months. In the base case it was assumed that the monthly probability that a fistula recurs after infliximab treatment was 18% per month for months 2-4, then decreased by 3% per month to the end of the 1-year time frame.

Based on the literature, the benefits from the initial infusion with infliximab were assumed to occur within the first month after infusion.

The effects of 6-mercaptopurine and metronidazole were assumed not to be additive or synergistic and metronidazole was assumed to provide the initial therapeutic benefit whilst 6-mercaptopurine would help maintain this benefit.

All health states were assumed to last for at least one cycle (1-month) with the exception of pancreatitis, which was assumed to last one week.

Neutropenia was not included as a side effect from 6-mercaptopurine and metronidazole in the model because it was assumed to have minimal effects on costs and patient preference weights.

**Measure of benefits used in the economic analysis**
The measure of benefit used in the economic analysis was the Quality-Adjusted Life Year (QALY). Standard gamble techniques were used to elicit the preference weights (utility), for the 11 health states used in the model, from two samples of respondents: a sample of 32 patients (17 with fistulae and 15 with no fistulae) with Crohn's disease and a sample of 20 healthy individuals.

Separate analyses were conducted using the utilities from these two samples. Differences in utilities between the two samples and between patients with Crohn's disease, with and without a history of fistulae, were assessed using a t-test.
Confidence intervals for sample means were calculated assuming a t-distribution.

**Direct costs**
An appendix to the paper reported costs and quantities separately. Direct costs to the hospital were included in the analysis. Direct costs of inpatient and outpatient hospital services for each health state were estimated. These included the cost of drugs, laboratory tests, diagnostic services, physician charges, clinic visits, surgical services and accommodation.

The estimation of unit costs was based on the University of Virginia (UVA) hospital cost-charge ratios. Charge data were obtained from the UVA Clinical Data Repository, an administrative database containing hospital and physician billing data for all inpatient and outpatient admissions to UVA between 1 July 1993 and 31 December 1999. Average total costs were reported in 1999 US dollars. The authors did not report the method used to adjust for inflation over the 6 year period covered by the UVA database. The authors excluded direct costs to other care providers on the basis that they would be consistent between the alternative interventions.

For infliximab strategies, the following costs for each health state were used: fistula = $8,000; reinfusion = $2,609; abscess = $1,985; persistent fistula = $99; persistent fistula and previous abscess = $99.

For 6-mercaptopurine and metronidazole strategies, the following total costs were reported: fistula = $992; paresthesias = $394; pancreatitis = $2,027; improved fistula = $168; persistent fistula = $267; fistula persisted when off medications = $99.

Costs were discounted at an annual rate of 3%.

**Statistical analysis of costs**
No statistical analysis of costs was reported.

**Indirect Costs**
Indirect costs were not included in the analysis. The authors reported that, although the indirect costs associated with the condition are recognised as significant burdens among patients with Crohn's disease, such costs are difficult to quantify monetarily, and they were assumed to be reasonably consistent among the three interventions.

**Currency**
US dollars ($). No currency conversions were reported.

**Sensitivity analysis**
One-way sensitivity analyses were performed on all cost, probability, and utility estimates in the model, as well as the time course for loss of response after infliximab. Each probability variable was tested over its 95% confidence interval. Cost data were varied by 25% and the effectiveness of infliximab was varied between 0% and 100%. A threshold analysis was performed on the costs of a single dose of infliximab. Tornado diagrams were used to identify influential variables and additional sensitivity analyses on incremental cost utility ratios were conducted.

**Estimated benefits used in the economic analysis**
The QALYs obtained from the preference weights (utilities) from the patients with Crohn's disease were:

- 6-mercaptopurine and metronidazole = 0.76 QALYs;
- 3 infliximab infusions plus 6-mercaptopurine and metronidazole as second line = 0.78 QALYs;
- infliximab with episodic reinfusion = 0.78 QALYs;
6-mercaptopurine and metronidazole plus infliximab as second line = 0.77 QALYs.

The QALYs obtained from the preference weights (utilities) from the healthy individuals were:
6-mercaptopurine and metronidazole = 0.82 QALYs;
3 infliximab infusions plus 6-mercaptopurine and metronidazole as second line = 0.84 QALYs;
infliximab with episodic reinfusion = 0.83 QALYs;
6-mercaptopurine and metronidazole plus infliximab as second line = 0.84 QALYs.

**Cost results**
The total cost for 6-mercaptopurine and metronidazole was $2,894.
The total cost for 3 infliximab infusions plus 6-mercaptopurine and metronidazole as second line was $10,003.
The total cost for infliximab with episodic reinfusion was $10,112.
The total cost for 6-mercaptopurine and metronidazole plus infliximab as second line was $6,664.

**Synthesis of costs and benefits**
Using preference weights from patients with Crohn's disease, the incremental cost-utility ratios for the base case were:

$355,450 per QALY for 3 infliximab infusions plus 6-mercaptopurine and metronidazole as second line versus 6-mercaptopurine and metronidazole (comparator);

$360,900 per QALY for infliximab with episodic reinfusion versus 6-mercaptopurine and metronidazole (comparator);

$377,000 per QALY for 6-mercaptopurine and metronidazole plus infliximab as second line versus 6-mercaptopurine and metronidazole (comparator).

Using preference weights from healthy individuals, the incremental cost-utility ratios for the base case were:

$355,450 per QALY for 3 infliximab infusions plus 6-mercaptopurine and metronidazole as second line versus 6-mercaptopurine and metronidazole (comparator);

$721,800 per QALY for infliximab with episodic reinfusion versus 6-mercaptopurine and metronidazole (comparator);

$188,500 per QALY for 6-mercaptopurine and metronidazole plus infliximab as second line versus 6-mercaptopurine and metronidazole (comparator).

The most influential variable in the model was the unit cost of infliximab. The threshold analysis on the cost of a single dose of infliximab for a 70kg person found that reducing the cost of infliximab from its 1999 wholesale price of $2,030 to $203 would reduce the incremental cost-utility ratio of infliximab with episodic reinfusion compared to 6-mercaptopurine and metronidazole to $36,050 per QALY.

The one-way sensitivity analysis showed that the model was also sensitive to the estimates for the monthly probability of paresthesias, utility for improved and persistent fistula health states, the monthly probability that a fistula improves after infliximab or 6-mercaptopurine metronidazole therapy.

A two-way sensitivity analysis that simultaneously varied the utility weights for persistent fistula after infliximab and after 6-mercaptopurine metronidazole treatments and for improved fistula after these therapies showed that incremental cost-utility ratios below $150,000 per QALY occur only if patients value an improved fistula after infliximab therapy much higher than after 6-mercaptopurine and metronidazole therapy.
Authors’ conclusions
The authors concluded that, based on the available data, all strategies had similar effectiveness in the Markov model presented, but infliximab was much more expensive than 6-mercaptopurine and metronidazole. The incremental benefit of infliximab for treating patients with Crohn's disease perianal fistulae over a period of 1-year may not justify the higher cost.

CRD COMMENTARY - Selection of comparators
A justification was given for the comparator used, namely that it represents traditional practice in the authors’ setting. You, as a user of this database, should decide if this is a widely used health technology in your own setting.

Validity of estimate of measure of effectiveness
The authors reported that a systematic review of the literature had been undertaken. Most of the methods and conduct of the review were satisfactorily reported. The authors did not report the sources used to identify primary studies, so it is not possible to determine whether a comprehensive search was undertaken. Effectiveness data to derive individual probability variables were combined using a fixed effects model. The authors did not report whether a weighting scheme was used to account for differences in sample sizes. However, the authors did excluded studies with sample sizes of fewer than 10 patients. The authors noted a number of limitations in the estimates of effectiveness. These included the use of a broadly defined clinical endpoint that included complete and partial closure of fistulae. This may bias the estimates of effectiveness if there are differences between the alternative interventions in the rates of complete closure. The authors also noted a lack of data, which meant that they had to make a number of assumptions. In addition, the authors reported that poor data quality was an issue. Sensitivity analysis was used to test the robustness of the results to uncertainty in the data used. The authors noted that further prospective studies are needed.

Validity of estimate of measure of benefit
The estimation of benefits was obtained from a standard gamble exercise with two samples, a group of patients with Crohn's disease and a group of healthy volunteers. The method used to derive the measure of health benefit, standard gamble, was appropriate. The authors did not report details of the particular standard gamble instrument used with respondents.

Validity of estimate of costs
All categories of costs relevant to the third-party payer perspective were included in the analysis. Some relevant direct and indirect costs were omitted. The authors noted that these costs were likely to be similar across the interventions. Costs and quantities were reported separately. The study included a comprehensive sensitivity analysis. The ranges used appear to be appropriate. The study reported that costs were discounted at a rate of 3%, even though the time frame for the study was less than one-year. In this instance discounting of costs was not necessary. Currency conversions were not performed. A cost-charge ratio was used to convert charge data to unit costs. The source of the cost-charge ratio was reported but the method used was not described. The use of a charge without an explanation of the conversion ratio to a unit cost may limit the generalisability of the studies findings to other settings outside the USA.

Other issues
The authors did not make comparisons of their findings with those from other studies. The issue of generalisability to other settings was addressed, in part, by the sensitivity analysis. The authors do not appear to have presented their results selectively. The study used a model based on a patient population with Crohn's disease and this was reflected in the authors’ conclusions.

The authors reported a number of further limitations to their study. Firstly, it is difficult to determine an appropriate endpoint in research involving treatment of patients with Crohn's disease fistulae. Also there was a lack of data on direct comparisons between medical treatments for fistula associated with Crohn's disease and the authors only had a short time period of the analysis. The authors suggested that there is a lack of long-term data on the safety and efficacy
of infliximab, which severely limited the evaluation of cost-effectiveness to a short time-period. They added that infliximab may appear more cost-effective over a longer time horizon by improving the relapse rate.

**Implications of the study**
The authors suggested that, at its current cost, the incremental cost-utility of infliximab for treating patients with Crohn's disease with perianal fistulae is greater than $350,000 per QALY. Infliximab can be considered a cost-effective alternative for the medical management of perianal fistula if society is willing to pay more than $350,000 for each QALY gained. The authors suggest that prospective studies directly comparing 6-mercaptopurine and metronidazole and infliximab are warranted.

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