Cost-effectiveness analysis of interferon beta in multiple sclerosis: a Markov process analysis

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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 beta-interferon (IFNB) for the preventive treatment of patients with multiple sclerosis (MS). IFNB is generally used to delay disease progression.

Type of intervention
Secondary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients with MS. The typical patient considered in the study was a 30-year-old female patient with initial relapsing-remitting-form (RRMF) of the disease.

Setting
The setting was a hospital. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness data were obtained from studies published between 1989 and 1998. The resource use and costs were estimated from studies published in 1998. The price year was 1998.

Source of effectiveness data
The effectiveness data were derived from a review of published studies. Authors' assumptions were also used in the decision model.

Modelling
A Markov model was used to estimate the costs and effectiveness of IFNB, compared with no preventive treatment, in a hypothetical cohort of 30-year-old female patients with initial RRMS and an initial expanded disability status scale (EDSS) score of 2.5. The overall time horizon of the model was the patient's lifetime and each cycle of the model lasted 3 years. An external opinion leader validated the methodology of the model structure and the assumptions.

Outcomes assessed in the review
The primary outcomes assessed from the published studies were the following transitional probabilities:

for stage I (EDSS 2.5 to 4.5), continuation after the first cycle of IFNB (8 MIU), progression with placebo, progression
with IFNB (8 MIU), and minimum and maximum values for progression with interferons;

for secondary progressive disease, for stage II (EDSS 4.5 to 7.5), progression with placebo and progression with IFNB (8 MIU); and

for stage III, progression from EDSS 8.5 to death.

The annual frequencies were also assessed for exacerbations for stage I and stage II, for both placebo and interferon. Finally, the utility values for several health states were estimated from a published study.

**Study designs and other criteria for inclusion in the review**
The primary studies for the transitional probabilities were all randomised controlled trials, while a cross-sectional study was used for utility values.

**Sources searched to identify primary studies**
Not stated.

**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 evidence on the transitional probabilities used in the decision model, and the utility values used to calculate the quality-adjusted life-years (QALYs) were derived from five primary studies.

**Methods of combining primary studies**
The studies were combined using narrative methods.

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

**Results of the review**
The transitional probabilities for stage I (EDSS 2.5 to 4.5) were:

- 0.920 for continuation after the first cycle of IFNB (8 MIU),
- 0.28 for progression with placebo,
- 0.20 for progression with IFNB (8 MIU), and
- 0.193 as the minimum and 0.219 as the maximum value for progression with interferons.

The transitional probabilities for secondary progressive disease were:

for stage II (EDSS 4.5 to 7.5), 0.5 for progression with placebo and 0.39 for progression with IFNB (8 MIU); and
for stage III, 0.31 for progression from EDSS 8.5 to death.

The annual frequencies for exacerbations were:

for stage I, 1.21 for placebo and 0.84 for interferon; and
for stage II, 0.64 for placebo and 0.44 for interferon.

The utility values ranged from 0 (dead) to 0.71.

The utility loss due to relapse was 0.5.

**Methods used to derive estimates of effectiveness**
The authors made some assumptions to populate the decision model, due to the lack of published data.

**Estimates of effectiveness and key assumptions**
The probability value from EDSS 8.5 to death was assumed to be 0. The authors assumed that disease progression after the actual follow-up period was the same whether patients did or did not receive preventive treatment in stage III of the disease (EDSS 7.5 to 9.5), and that there was no difference in mortality in the two study groups. They also assumed that non-compliance occurred only during the first cycle of the decision model, and that patients in stage III did not experience any exacerbation and did not receive any benefit from IFNB.

**Measure of benefits used in the economic analysis**
The benefit measure in the economic analysis was QALYs. Utility weights were derived from a published study. No discounting of the benefits was performed.

**Direct costs**
The lifetime costs were discounted using a 6% rate from the second year onwards. The unit costs and the quantities of resources were not reported. The health services included in the economic evaluation were for medication and consultations. The cost/resource boundary for the direct costs was that of the NHS. The total expected costs of the interventions were calculated using modelling. The costs and quantities were estimated from two cross-sectional studies. All of the costs were inflated to 1998 values from 1996 using a 4.3% inflation correction.

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

**Indirect Costs**
A 6% discount rate was used as the lifetime costs were estimated. Neither the unit costs nor the quantities of resources used were reported. The non-medical costs examined in the analysis were workdays lost, transportation, community assistance and home modifications. The cost/resource boundary adopted was that of society. The friction cost method was used to calculate the indirect costs, assuming a productivity loss that was 80% of the average value of a worker's productivity during the "friction period". The time lost by inactive patients was considered as leisure time lost and was valued at 40% of the average wage in UK. The care-giver's time was also included in the analysis. The authors made some assumptions on time lost due to relapse. The source of the cost data was the Office for National Statistics Earnings. The price year was 1998.

**Currency**
UK pounds sterling (£).
Sensitivity analysis
Several univariate sensitivity analyses were conducted to assess the impact of variations in model inputs on the estimated cost-utility ratio. Most of the model parameters (costs and baseline probabilities) were varied. In addition, the use of different discount rates for both the costs and QALYs was also tested.

Estimated benefits used in the economic analysis
The total QALYs gained were 28.2 with IFNB and 24.9 with no treatment. The difference of 3.3 QALYs per patient favoured the IFNB treatment.

Cost results
From the NHS perspective, the total discounted (undiscounted) costs were 221,436 (659,980) with IFNB and 51,241 (210,824) with no treatment. There was an extra cost of 170,222 (210,824) with IFNB.

From the societal perspective, the total discounted (undiscounted) costs were 473,115 (1,530,717) with IFNB and 322,499 (1,209,409) with no treatment. There was an extra cost of 150,616 (321,308) with IFNB.

Synthesis of costs and benefits
An incremental analysis was conducted to combine the costs and QALYs of the IFNB over no treatment. The incremental discounted cost per QALY was 51,582 from the perspective of the NHS. The sensitivity analyses showed that the estimated cost per QALY was sensitive to the discount rate, cost of IFNB, and disease progression.

Authors’ conclusions
Preventive treatment with beta-interferon (IFNB) in patients with multiple sclerosis (MS) may not be fully cost-effective from the perspective of the National Health Service (NHS) in the UK. However, IFNB proved to be an effective treatment as it led to more QALYs than no treatment.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. No preventive treatment was selected, as the aim of the study was to assess the active value of the intervention. You should decide whether it represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness was conducting using several published studies. However, a formal review of the literature was not undertaken and effectiveness estimates (transitional probabilities) were combined using narrative methods. It would appear that the primary studies used to estimate the transitional probabilities were all randomised controlled trials. The authors did not report any criteria to ensure the validity of the primary studies. They also did not state whether they considered potential differences among primary studies when estimating the effectiveness. Some assumptions were also used in the decision model, although sensitivity analyses were conducted to assess the impact of these assumptions and the baseline estimations on the study results.

Validity of estimate of measure of benefit
The benefit measure used in the economic analysis was QALYs, which was appropriate for the study treatment. A Markov model was used to derive QALYs, whose utility weights were based on published data. The authors noted that the adverse effects of the study treatment did not affect the utility values. This could have represented a limitation of the analysis. The use of QALYs enhances the comparability of the cost-effectiveness of the study treatment with that of other interventions funded in the health care system.
Validity of estimate of costs
The analysis of costs was carried out from two perspectives, the NHS and society. The authors stated that all the relevant costs were included in the analysis. However, a detailed costing was not provided and neither the unit costs nor resource quantities were reported. The cost estimation relied mainly on published studies. The price year was appropriately reported as the estimated costs were inflated to 1998 values. Although the costs were treated deterministically in the base-case, some sensitivity analyses were conducted. The authors acknowledged that costs for the treatment of adverse events of interferon were not considered, thus the overall costs of the study treatment may have been underestimated.

Other issues
The authors made several comparisons of their findings with those from other studies. The issue of the generalisability of the study results to other settings was not addressed and the overall external validity of the analysis was low, also due to the fact that the unit costs and quantities of resources were not reported. The study referred to patients with MS using IFNB, 8 MIU only, and this was reflected in the conclusions of the study. The authors reported some limitations of the analysis. These mainly arose from the fact that the primary studies used to derive the effectiveness evidence may not represent real clinical practice.

Implications of the study
Although the analysis showed that treatment with IFNB led to a high cost-effectiveness ratio, the authors stressed that development of clinical guidelines for prospective data collection may be useful to validate the findings of the present study.

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