Long-term cost effectiveness of interferon-beta-1a in the treatment of relapsing-remitting multiple sclerosis: an econometric model

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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 subcutaneous interferon-beta-1a (IFNB-1a) (Rebif; Serono, Geneva), 44 microg three times weekly, in the treatment of relapsing-remitting multiple sclerosis (MS).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with relapsing-remitting MS.

Setting
The setting was secondary care. The economic study was carried out in the UK and France.

Dates to which data relate
Data were collected from the Prevention of Relapses and Disability by INFB-1a Subcutaneously in Multiple Sclerosis (PRISMS) study. The dates of the trial were not reported, although the authors obtained data from papers concerning this trial that had been published between 1999 and 2001. The costs were taken from a study published in 1998. The price year was 2000.

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

Link between effectiveness and cost data
The costing was carried out retrospectively on a different sample of patients to that used in the effectiveness study.

Study sample
A parent study was used for the effectiveness analysis (see Other Publications of Related Interest). The information reported here relates only to that information reported in the current study. Further details should be obtained from the parent study.

The authors did not report details of sample selection and, therefore, did not give details of whether power calculations were carried out to estimate the impact of chance on the results. A total of 560 patients entered the study. Of these, 187
were randomised to initially receive placebo, 189 were randomised to receive IFNB-1a 22 microg three times weekly, and 184 were randomised to receive IFNB-1a 44 microg three times weekly. After 2 years, patients remaining in the trial who initially received placebo were randomised to receive IFNB-1a, either 22 microg three times weekly (n=85) or 44 microg three times weekly (n=87). There were no reports of patients excluded for any reason or refusals to participate.

Study design
The analysis was based on a randomised placebo-controlled trial. The method of randomisation was not reported. The participants were followed for 4 years, with clinical assessments every 3 to 6 months and annual assessments of disease activity by magnetic resonance imaging. Of the 560 patients that entered the study, 90% (506) remained after 2 years and 79% (445) after 4 years. Both patients and clinicians were reported to be blinded.

Analysis of effectiveness
At least part of the analysis was carried out according to intention to treat. The primary health outcomes were the coefficients estimated by the regression model. The authors were concerned with outcomes according to the Expanded Disability Status Scale (EDSS), a measure of well-being specific to MS. The area under the EDSS score-time curve was used as a measure of disability, with the effectiveness of treatment being expressed as EDSS-months of treatment prevented. The authors did not report summary statistics for the patient groups, and so were unable to draw comparisons and look for potentially confounding variables. This level of detail may have been reported in the parent study.

Effectiveness results
The authors reported that the "slope" coefficients of the regression analysis reflected the disability evolution rate in each treatment group.

The baseline EDSS score coefficient was 1.2044 (standard error, SE=0.01947, p<0.0001).

The coefficient for IFNB-1a 44 microg was 1.5835 (SE=0.01388, p<0.0001).

The coefficient for placebo was 1.9865 (SE=0.0349, p<0.0001).

Clinical conclusions
The authors reported that an analysis of variance confirmed that the variables used in the model were significantly related to the area under the curve of the EDSS. The model accounted for 74.4% of the variance in the effectiveness measure.

Modelling
An econometric time series regression model was developed to project disability outcomes over 10 and 20 years. The model incorporated both quantitative and qualitative variables.

Measure of benefits used in the economic analysis
The authors used EDSS-months of disability prevented as their summary measure of health benefit.

Direct costs
The authors did not report the perspective from which the costing analysis was carried out. The costs for patients receiving standard care were derived from a published source for both the UK and France. As the costs were taken from this source, it was unclear what elements of cost were included or excluded. Regression models for medical cost data were developed using baseline and cumulative costs. Although not explicitly stated, it would appear that all the
costs were discounted at a rate of 6%. This was appropriate as the model extended over 10- and 20-year time horizons. The price year was 2000.

**Statistical analysis of costs**
The authors used a regression analysis incorporating SE, t-values and p-values to assess the influence of baseline EDSS costs, time of measurement, and the presence or absence of treatment with IFNB-1a, on the overall cost.

**Indirect Costs**
It was unclear whether the indirect costs were incorporated in the analysis.

**Currency**
UK pounds sterling () and Euros (Euro).

**Sensitivity analysis**
There was no report of sensitivity analyses being carried out.

**Estimated benefits used in the economic analysis**
After 10 years of treatment, patients in the IFNB-1a group experienced 484 EDSS-months of disability while placebo patients experienced 605 EDSS-months.

After 20 years of treatment, patients in the IFNB-1a group experienced 1,266 EDSS-months of disability while placebo patients experienced 1,587 EDSS-months.

After 10 years of treatment, IFNB-1a saved 121-months of disability in comparison with placebo.

**Cost results**
For the UK, the total cost over 10 years was 243,141 (Euro 393,074) for IFNB-1a and 188,159 (Euro 304,223) for placebo. The total cost over 20 years was 448,602 (Euro 725,180) for IFNB-1a and 377,268 (Euro 609,938) for placebo.

For France, the total cost over 10 years was Euro 201,338 for IFNB-1a and Euro 114,803 for placebo. The total cost over 20 years was Euro 364,589 for IFNB-1a and Euro 244,599 for placebo.

The authors reported the "slope" coefficients of the regression analysis in full for all variables.

**Synthesis of costs and benefits**
For the UK, the cost per EDSS-month saved by treatment with IFNB-1a was 453 (Euro 732) over a 10-year horizon and 222 (Euro 359) over a 20-year horizon.

For France, the cost per EDSS-month saved by treatment with IFNB-1a was Euro 712 over a 10-year horizon and Euro 374 over a 20-year horizon.

**Authors' conclusions**
Interferon-beta-1a (IFNB-1a) 44 microg is cost-effective in the treatment of relapse-remitting multiple sclerosis (MS). The treatment becomes increasingly cost-effective over time.
CRD COMMENTARY - Selection of comparators
The authors compared subcutaneous IFNB-1a, 44 microg three times weekly, with placebo. A secondary analysis considered a smaller dose of interferon. Standard practice in the authors' setting was unclear, although it was reported that NICE had issued guidance on the usage of interferon. You should decide if this represents a valid comparison in your own setting.

Validity of estimate of measure of effectiveness
The authors used an econometric time series regression model to assess effectiveness, arguing the benefits of this approach over a Markov modelling approach. Information was taken from a single placebo-controlled randomised trial, which was appropriate for the study question and helped minimise systematic differences between the patient groups. Relatively few details of the parent study were reported, as further details had been published elsewhere (see Other Publications of Related Interest). In particular, there was no comparison of the groups at baseline. This prevents the reader from assessing whether there were systematic differences between the groups that might have contributed to the results. Appropriate statistical analyses were performed during the regression analysis to assess the importance of the variables included in the model.

Validity of estimate of measure of benefit
The authors used cumulative EDSS-months of disability as their summary measure of health benefit. This is a clinically meaningful measure that incorporates temporary and permanent changes in disease status. The authors discussed some limitations of this measure. A more generic measure such as quality-adjusted life-years (QALYs) would have made the results more broadly comparable.

Validity of estimate of costs
A perspective for the costing analysis was not reported, thus it was not possible to assess whether all the relevant costs were included. Moreover, as the costing was taken from a published study, only limited details were actually reported to allow the reader to assess which perspective might have been relevant. Although appropriate statistical analyses were carried out, without further detail it is difficult to assess the cost-drivers. Both the discount rate and the price year were reported.

Other issues
The authors noted the difficulty in comparing their own findings with those of other authors, owing to differences in the outcome measure used. This difficulty might have been avoided with the use of QALYs. The issue of generalisability was not addressed, although the modelling nature suggests that the basic model can be applied in different settings with other country-specific data. The conclusions drawn reflected the study questions and also the results presented. Limitations of the study included assumptions behind the modelling process, as acknowledged in the authors' discussion. The discussion also included a detailed summary of reasons why the regression modelling approach is preferable to other available techniques, such as Markov modelling.

Implications of the study
The authors did not make any specific recommendations for policy or practice, although they did express a hope that policy-makers would consider the approach described when conducting further pharmacoeconomic evaluations in a similar setting. Further suggested work included development of the econometric model to focus on possible ways to take the absolute disability level reached by a given patient into consideration.

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