A cost-utility analysis of mitoxantrone hydrochloride and interferon beta-Ib in the treatment of patients with secondary progressive or progressive relapsing multiple sclerosis

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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
Three strategies for the treatment of patients with secondary progressive or progressive relapsing multiple sclerosis (MS) were investigated. The strategies were standard supportive care without disease-modifying therapy (e.g. corticosteroids and other medications to treat symptoms and complications), mitoxantrone hydrochloride (MHCl) administered every 3 months, and interferon (IFN) beta-1b administered every other day.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with secondary progressive or progressive relapsing MS with an Expanded Disability Status Scale (EDSS) of 3.0.

Setting
The setting of the study was unclear, but it appears to have been community and secondary care. The study was conducted in USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1998 and 2002. The resource use data were derived from studies published between 1998 and 2001. The price year was 2000.

Source of effectiveness data
The effectiveness data were derived from a review of published studies, supplemented by authors' assumptions.

Modelling
A Markov model was developed to predict the utility and costs of care for patients receiving each of the three treatment strategies. In this model, simulated patients moved into and out of defined health states over time, with the model being run for 10 annual cycles. For the purpose of the model, patients were grouped in EDSS point increments of 1. The authors assumed that patients progressed less than 1 EDSS point per year.

Outcomes assessed in the review
The outcomes assessed were:
the transition probability and annual risk of having a relapse with routine supportive care, MHCI and IFN beta-1b;

the relative risk (RR) compared with supportive care;

the utilities associated with different stages of MS (as measured by the EDSS); and

the utility loss with each relapse associated with different stages of MS (as measured by the EDSS).

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

Journal articles published in English between 1966 and July 2002 were considered for inclusion if they addressed controlled, randomised, or clinical trials of either MHCI or IFN beta-1b for the treatment of secondary progressive or progressive relapsing MS, and if they contained clinical, epidemiologic, or humanistic information relevant to the introduction or discussion.

**Sources searched to identify primary studies**

MEDLINE was searched using the terms "mitoxantrone and multiple sclerosis", "interferon and multiple sclerosis", "mitoxantrone and cost", "interferon and cost", and "multiple sclerosis and utility". In addition, the bibliographies of pertinent articles (clinical trials or reviews) were scanned for additional references. Any study that came to the authors' attention after the literature search was also reviewed for appropriateness. Additional MEDLINE searches were performed for specific epidemiologic and other necessary estimates for the model.

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

Humanistic analyses were only considered if they contained estimates of utility for MS according to EDSS scores, and preferably had estimates specific to secondary progressive and/or progressive relapsing MS.

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

Not reported.

**Number of primary studies included**

The authors reported that the effectiveness data were derived from three studies. The efficacy of MHCI in preventing relapses and slowing disease was determined from the largest clinical trial of MHCI, which assessed 188 patients for the treatment of MS. Clinical inputs for IFN beta-1b were estimated using data from a controlled randomised trial that assessed 718 patients. The reported toxicities for both treatments were obtained from the respective products' package inserts, although the authors did not report these estimates. Utility measures for each health state in the model were abstracted from a single study (Parkin et al., see Other Publications of Related Interest). It was unclear whether additional data derived from other studies were used to populate the model.

**Methods of combining primary studies**

Not applicable.

**Investigation of differences between primary studies**

Not applicable.

**Results of the review**

The routine supportive care transition probability was 0.236.

The MHCI transition probability was 0.152. The RR of MHCI compared with supportive care was 0.644.
The IFN beta-1b transition probability was 0.185. The RR of IFN beta-1b compared with supportive care was 0.784.

The supportive care annual risk of having a relapse was 0.6.

The MHCI annual risk of having a relapse was 0.207. The RR of MHCL compared with supportive care was 0.346.

The IFN beta-1b annual risk of having a relapse was 0.413. The RR of IFN beta-Ib compared with supportive care was 0.688.

The utilities associated with the various MS health states were 0.71 (EDSS score 3), 0.66 (EDSS score 4), 0.52 (EDSS score 5), 0.49 (EDSS score 6), and 0.35 (EDSS score 7).

The utility loss with each relapse was 0.0417 irrespective of EDSS score.

**Methods used to derive estimates of effectiveness**
The authors supplemented the results of the review with several assumptions of their own.

**Estimates of effectiveness and key assumptions**
The authors assumed that, with MHCL, the rate of disease progression and effect on relapses would equal those seen with routine supportive care after 24 months. They also assumed that, owing to the transient nature of urinary tract infections, these would not result in a substantial or measurable reduction of utility. Finally, it was assumed that because dose-limiting toxicities had not been associated with IFN beta-1b, the patients would continue to receive that therapy and experience beneficial effects on disease progression and relapses for up to 10 years.

**Measure of benefits used in the economic analysis**
The measure of benefits used was the number of quality-adjusted life-years (QALYs) gained. Utility measures for each Markov state in the model were abstracted from a study conducted by Parkin et al. (see Other Publications of Related Interest). The utilities were discounted at a rate of 5% per year.

**Direct costs**
Resource use and costs were not reported separately. The direct costs included were those of the insurer. These comprised:

- the costs associated with medical remission and relapse, which were estimated from a published study and then adjusted by severity of the condition;
- the costs associated with the administration of IFN beta-1b and MHCL, which were derived from the manufacturers’ package inserts;
- the costs associated with treating urinary tract infections in patients treated with MHCL, which were estimated using fee-for-service prescription claims data from the Oregon Medicaid programme; and
- the costs related to therapy intake, such as referrals to the oncology unit, echocardiograms, pre-medication with an antiemetic, and determination of clinical tests as recommended by the package insert.

Outpatient charges from these tests were estimated from a database containing information on typical allowable health maintenance organisation and point-of-service in-network charges in seven metropolitan areas across the USA. Medication costs were estimated at 80% of the average wholesale price. All the costs were adjusted for inflation for the year 2000 using medical inflation rates from the US Bureau of Labour Statistics. Discounting was relevant, as the costs were incurred during 10 years, hence all future costs were discounted at a rate of 5% per annum. The average costs were reported.
Statistical analysis of costs
The costs were treated as point estimates (i.e. the data were deterministic).

Indirect Costs
The authors included the indirect costs relating to the lost wages of patients and caregivers in the analysis. The indirect costs were derived from published studies identified in the review of the literature, and were adjusted by severity of disease (as measured by the EDSS). All the costs were adjusted for inflation for the year 2000 using medical inflation rates from the US Bureau of Labour Statistics. Discounting was relevant, as the costs were incurred during 10 years, hence all future costs were discounted at a rate of 5% per annum. The average costs were reported.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were conducted to assess uncertainty in the model. The authors conducted a one-way sensitivity analysis on all variables in the model. The cost inputs were varied from 50 to 200% of the base-case values. Confidence intervals from the trials were used to conduct the sensitivity analysis for the effectiveness of therapy. The discount rates were varied from 0 to 10%.

A Monte Carlo simulation was performed, so as to characterise the overall variability of the model. The simulation was run 100,000 times to forecast differential costs, utilities and cost-utility ratios between the three treatment strategies.

The authors also undertook scenario analyses, whereby the assumptions about the dosage and effectiveness of MHCI were varied.

Estimated benefits used in the economic analysis
During the 10-year period, 4.9650 QALYs were gained with supportive care, 5.0860 with MHCI, and 5.1702 with IFN beta-1b.

Cost results
During the 10-year period, the costs from the insurer's (societal) perspective $46,331 ($383,520) with supportive care, $53,378 ($378,464) with MHCI, and $115,833 ($433,932) with IFN beta-1b.

Synthesis of costs and benefits
The costs and benefits were combined using an incremental cost-utility ratio (i.e. the additional cost per QALY gained).

From the insurer's perspective, the incremental cost-utility ratio of MHCI therapy compared with routine care was $58,272 per QALY gained. From a societal perspective, MHCI was more effective and less costly than supportive care.

From the perspectives of insurers and society, the cost-utility ratios of IFN beta-1b compared with routine supportive care were $338,738 (insurer) and $245,700 (society) per QALY gained, respectively. When compared with MHCI, IFN beta-1b had incremental cost-utility ratios of $741,331 (insurer) and $658,402 (society) per QALY gained.

The results of the sensitivity analysis showed that the cost-utility ratios for MHCI were sensitive to the acquisition and administration costs of therapy, and to the effectiveness at slowing disease progression. The cost-utility ratios for IFN beta-1b were not sensitive to any of the variables included in the model.

Authors' conclusions
Mitoxantrone hydrochloride (MHCl) is likely to be a cost-effective treatment for patients with secondary progressive or progressive relapsing multiple sclerosis (MS) from an insurer's perspective, and it was cost-saving from a societal perspective. Interferon (IFN) beta-1b is not likely to be an efficient treatment using the conventional comparisons for cost-effectiveness.

CRD COMMENTARY - Selection of comparators
A justification was given for the comparators used. IFN beta-1b and supportive care are both current practice in the USA, and have been approved by the US Food and Drug administration for the treatment of patients with MS. You should decide if these are widely used health interventions in your own setting.

Validity of estimate of measure of effectiveness
The authors performed an adequate review of the literature, identifying studies through electronic searches and hand searches. It would appear that the review was conducted systematically, so as to identify all relevant research and minimise biases. Further, the authors also reported the methodology they used in their review by providing the sources searched, the search strategy used and the inclusion criteria for the review. However, as the authors only provided data from three studies, it was unclear whether additional data derived from other studies were used to populate the model. The authors made several assumptions of effectiveness, but these estimates were appropriately investigated in a sensitivity analysis.

Validity of estimate of measure of benefit
The estimation of benefits was modelled. The instrument used to derive a measure of health benefit (i.e. the Markov model) was appropriate. Since the benefits could be incurred during 10 years, all future benefits were discounted at a rate of 5% per annum.

Validity of estimate of costs
All the categories of cost relevant to the perspective adopted were included in the analysis. It would appear that no relevant costs were omitted. The cost of adverse events was not included as they were self-limiting. The costs and the quantities were not reported separately, which will limit the generalisability of the authors' results. The cost estimates were derived from published studies and other sources, such as Medicaid charges. The authors did not report clearly the sources used to obtain estimates of each type of cost, nor how adjustments for disease severity were undertaken. However, a suitable sensitivity analysis of the costs was conducted using appropriate ranges. Since the costs were incurred during 10 years, discounting was relevant and was appropriately performed. Charges were used to proxy prices, hence the real cost of the interventions may vary from that charged to institutions such as Medicaid. The price year was reported, which will aid any possible inflation exercises.

Other issues
The authors reported that no US cost-effectiveness or cost-utility studies of IFN beta-1b in secondary progressive MS had been undertaken. However, they compared the results from their study with those from two studies, one within a UK setting (Forbes et al.) and another undertaken in Sweden (Kobelt et al.) (see Other Publications of Related Interest). The authors found similar results to the UK study which concluded that IFN beta-1b was not cost-effective. However, both series of results were in direct contrast with those from the Swedish study, which found that the incremental cost-utility of IFN beta-1b was $39,250 per QALY gained. The issue of generalisability to other settings was partially addressed in the sensitivity analysis. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis.

The authors reported a number of further limitations to their study. First, it was difficult to obtain economic data on the cost of MS in the USA. The authors used several sources of cost data, some of them from Canada, which might not be generalisable to the USA. However, appropriate sensitivity analyses were performed to test the variability in these estimates. Second, the utility estimates were derived from a study with a small sample size (n=89), the majority of which were female. Third, no study had assessed the differences in utility scores for each EDSS state. Fourth, the
authors extrapolated intermediate data to a 10-year timeframe. Finally, there is considerable controversy surrounding the appropriate use of decision modelling in MS, owing to the limitations of using EDSS scores, and regarding how far into the future models should predict outcomes.

**Implications of the study**
The authors reported that their analysis had potentially important implications for policy implementation. However, they also reported that decisions about which agent to use for each patient should be considered in the light of the treatment's adverse-event profile, the method of administration, and the patient's preferences for these factors.

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None stated.

**Bibliographic details**

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**Other publications of related interest**


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