Cost-effectiveness of four immunomodulatory therapies for relapsing-remitting multiple sclerosis: a Markov model based on long-term clinical data

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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 study examined five treatments for patients with relapsing-remitting multiple sclerosis (MS). These comprised symptomatic management (physical therapy and pharmacological treatment for symptom management) alone, or symptomatic management supplemented by four alternative immunomodulatory therapies. The immunomodulatory therapies were subcutaneous (SC) glatiramer acetate (GA) and three beta-interferons (IFNs), specifically, intramuscular (IM) IFN beta-1a, SC IFN beta-1a and SC IFN beta-1b.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis and cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with relapse-remitting MS.

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

Dates to which data relate
The clinical data and some information on resource use were derived from studies published between 1987 and 2005. The price year was 2005.

Source of effectiveness data
The clinical and epidemiological data used in the decision model were:

- the relapse and disease progression rates,
- the mortality rates,
- the initial patient distribution among EDSS health states,
- the incidence of neutralising antibodies (NAbs), and
- the effectiveness of treatment.

Modelling
A Markov model was constructed to simulate the natural history of disease and the impact of the five treatments on clinical and economic outcomes. The time horizon of the model was lifetime, and the cycles were monthly. The health states of the model were based on the Kurtzke Expanded Disability Status Scale (EDSS), which defined seven health states for patients with relapse-remitting MS:

- EDSS 0.0 - 2.5: no or few limitations in mobility;
- EDSS 3.0 - 5.5: moderate limitations in mobility;
- EDSS 6.0 - 7.5: walking aid or wheelchair required;
- EDSS 8.0 - 9.5: restricted to bed;
- death (natural causes or EDSS 10);
- relapse EDSS 0.0 - 2.5: relapse with a change in disability within EDSS 0.0 - 2.5; and
- relapse EDSS 3.0 - 5.5: relapse with a change in disability within EDSS 3.0 - 5.5.

The point at which patients transformed from relapse-remitting MS to secondary progressive MS was not specified in the model, but it was assumed that this transformation took place between EDSS 3.0 - 5.5 and EDSS 6.0 - 7.5. Switching among the immunomodulatory therapies was not permitted in the model. Patients discontinuing immunomodulatory therapy were assigned the transition probabilities for relapse and disease progression used in the symptom management arm. A simplified structure of the decision model was represented graphically.

**Sources searched to identify primary studies**
The initial patient distribution among EDSS health states was derived from a Web survey of patients treated with immunomodulatory therapies. Relapse and disease progression from the symptom management arm came from natural history studies. Mortality rates came from age- and gender-specific national statistics. Relapse and disease progression rates for immunomodulatory therapies came from randomised controlled trials (RCTs), prospective extensions of the clinical trials, and long-term follow-up studies. Some assumptions were also made.

**Methods used to judge relevance and validity, and for extracting data**
The clinical data were derived from the literature, but no details of any systematic review were provided. Information on the methods used to extract and combine the primary estimates was not reported. However, there was extensive information on some clinical trials used as primary studies. The authors stated that the issue of differences among the RCTs was also taken into account, assuming a fixed patient population.

**Measure of benefits used in the economic analysis**
The summary benefit measures used were the life-years (LYs), quality-adjusted life-years (QALYs), number of years spent in EDSS 0.0 - 5.5 (less severe relapse-remitting MS states), and the number of years spent relapse-free. The benefits were discounted at an annual rate of 3%. All benefits were derived from the decision model. Utility weights required to calculate QALYs were obtained from the published literature and were associated with each health state. Utility decrements were associated with each relapse. No details of the methods or instruments used to obtain the utility weights in the original studies were provided.

**Direct costs**
The analysis of the costs was carried out from a societal perspective. It included the medical costs associated with immunomodulatory therapies and health state-specific MS-related medical services. Specifically, the categories of costs included in the latter category were the costs of inpatient care, outpatient care, community services, alterations and equipment, informal care, and medications used to manage the symptoms of MS. The costs of immunomodulatory therapies included acquisition costs for the recommended dosing schedule, days supply per prescription, and patient co-
payment. Estimates were based on patient compliance and the proportion of patients discontinuing therapy. The unit costs and the resource quantities were not presented separately for most items. Resource use was estimated using data derived from published studies, including RCTs and the Web survey of patients treated with immunomodulatory therapies. The costs were estimated from wholesale acquisition prices, the Drug Topics Red Book, Current Procedural Terminology, and diagnosis-related groups. The costs were incurred over a long timeframe and an annual discount rate of 3% was used. All costs were reported in 2005 prices.

Statistical analysis of costs
The costs appear to have been treated deterministically in the base-case.

Indirect Costs
A societal perspective was adopted, thus productivity losses were appropriately included in the analysis. Days of missed work were derived from the literature and were then multiplied by an hourly wage. Some assumptions were required to derive these estimates. For example, patients in the most severe EDSS health states (EDSS >5.5) were assumed not to be employed. The unit costs and the resource quantities were not presented separately. As in the analysis of the costs, an annual discount rate of 3% was applied and 2005 prices were used.

Currency
US dollars ($).

Sensitivity analysis
The issue of uncertainty was extensively addressed in a univariate sensitivity analysis, where model inputs were varied using plausible published ranges or over +/- 25% ranges. The model inputs under examination were:

- health state and relapse state utilities;
- symptomatic treatment costs, health state costs and drug costs;
- percentage employed and work days saved;
- percentage reductions in relapse and disease progression rates in the first 2 years of therapy;
- changes in relapse and disease progression over time;
- change in treatment discontinuation over time;
- EDSS distribution;
- incidence of NAbs;
- change in NAbs over time; and
- discount rates.

Scenario analyses were also performed to take changes in multiple parameters into account. The robustness of the base-case results to variations in health state utilities was further investigated in three analyses. In one analysis all utility values were changed by a relative +/- 25%. In a second analysis the utility values in the base-case model were replaced with European-derived utilities used in previous economic evaluations. In the final analysis only the disutility values associated with the relapse health states were changed by a relative +/- 25%.

Estimated benefits used in the economic analysis
Over a patient's lifetime, the expected average number of years spent in EDSS 0.0 - 5.5 was 12.28 with symptom management, 14.92 with SC GA, 14.71 with IM IFN beta-1a, 14.29 with SC IFN beta-1a and 14.54 with SC IFN beta-1b.

The expected average number of years spent relapse-free was 11.42 with symptom management, 14.67 with SC GA, 14.24 with IM IFN beta-1a, 13.98 with SC IFN beta-1a and 14.15 with SC IFN beta-1b.

The expected LYs were 14.791 with symptom management, 14.819 with SC GA, 14.818 with IM IFN beta-1a, 14.815 with SC IFN beta-1a and 14.817 with SC IFN beta-1b.

The expected QALYs were 9.081 with symptom management, 9.303 with SC GA, 9.285 with IM IFN beta-1a, 9.279 with SC IFN beta-1a and 9.284 with SC IFN beta-1b.

**Cost results**

Over a patient's lifetime, the expected total costs were $295,586 with symptom management, $352,760 with SC GA, $364,267 with IM IFN beta-1a, $377,996 with SC IFN beta-1a and $358,509 with SC IFN beta-1b.

More than 95% of total costs in the symptom management arm and more than 70% in the four immunomodulatory therapy arms were MS-related medication costs.

**Synthesis of costs and benefits**

Incremental cost-effectiveness ratios and cost-utility ratios were calculated in order to combine the costs and benefits of the immunomodulatory therapies over management symptom.

In comparison with symptom management, the incremental cost per years spent in EDSS 0.0 - 5.5 was $21,667 with SC GA, $28,293 with IM IFN beta-1a, $41,008 with SC IFN beta-1a and $27,860 with SC IFN beta-1b.

In comparison with symptom management, the incremental cost per years spent relapse-free was $17,599 with SC GA, $24,327 with IM IFN beta-1a, $32,207 with SC IFN beta-1a and $23,065 with SC IFN beta-1b.

In comparison with symptom management, the incremental cost per LY gained was $2,076,622 with SC GA, $2,588,087 with IM IFN beta-1a, $3,378,626 with SC IFN beta-1a and $2,452,616 with SC IFN beta-1b.

In comparison with symptom management, the incremental cost per QALY gained was $258,465 with SC GA, $337,968 with IM IFN beta-1a, $416,301 with SC IFN beta-1a and $310,691 with SC IFN beta-1b.

Overall, the model suggested that patients on SC GA experienced better cost-effectiveness ratios than patients on any of the three beta-IFNs. In general, patients on SC GA were associated with lower costs and similar benefits than patients on the beta-IFN strategies.

The results of the sensitivity analysis showed that the base-case results were sensitive to variations in health state utilities, the percentage reduction in disease progression rates in the first 2 years' therapy used to estimate immunomodulatory therapy treatment effects, the model time horizon, and immunomodulatory therapy acquisition costs. However, the incremental cost per QALY for the immunomodulatory therapies compared with symptom management was higher than $200,000 in most situations.

**Authors' conclusions**

The strategy of subcutaneous (SC) glatiramer acetate (GA) was the most cost-effective immunomodulatory regimen for patients with relapse-remitting multiple sclerosis (MS) among the four therapies available. In addition, it led to better health outcomes in comparison with symptom management alone. However, none of the immunomodulatory therapies proved to be cost-effective compared with symptom management alone when using standard thresholds. The results of the analysis were highly sensitive to a number of model parameters.
CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear and appropriate. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were derived from published sources, but no systematic search for data was reported. The authors did not report the methods and conduct of a review of the literature. Information about the design of several sources was provided. It should be noted that clinical trials and long-term longitudinal studies usually have a high internal validity. The authors performed extensive sensitivity analyses to overcome the issue of uncertainty in the clinical parameters. The authors stated that a limitation of the effectiveness data was the lack of published head-to-head clinical trials. It is not clear which methods were used to deal with this issue.

Validity of estimate of measure of benefit
Both disease-specific and generic benefit measures were used in the analysis. All benefits were modelled using the Markov model. Discounting was appropriately performed and the impact of variations in the discount rates was investigated in the sensitivity analysis. Details of the derivation of utility weights were not reported. QALYs and LYs have the advantage of being comparable with the benefits of other health care interventions.

Validity of estimate of costs
The analysis of the costs was consistent with the authors' stated perspective. Productivity costs played a minor role in the economic analysis, which was mainly driven by disease-related medical costs. The sources of the costs were reported for all items, but limited information on unit costs and quantities of resources used was given. In effect, most costs were presented as macro-categories and a detailed breakdown of the cost items was not given. This could limit the possibility of replicating the economic analysis in other settings. Statistical analyses were not performed, but the impact of varying some key cost estimates was tested in the sensitivity analysis. The price year was reported, which will simplify reflation exercises in other time periods.

Other issues
The authors reported that the results of a previous economic evaluation differed from the findings of the current study. The authors stated that these discrepancies might have been due to the underlying methodology used to model MS in the two studies. This was apparent from the use of utility values. However, other published economic evaluations on MS therapies had shown similar findings to this study. The results of the analysis were presented clearly, especially those from the sensitivity analysis which were illustrated using a tornado diagram. The authors noted that the analysis did not take the potential impact of therapy-related adverse events into consideration. The authors also discussed the fact that their cost-effectiveness estimates were far above the commonly used threshold of $50,000 per QALY as a benchmark for cost-effectiveness. However, it was highlighted that several interventions above this threshold have been deemed valuable by decision-makers. Finally, the authors discussed some drawbacks to their analysis, which have already been highlighted in the relevant fields above.

Implications of the study
The authors pointed out that future studies should be based on head-to-head comparisons of immunomodulatory therapies for the treatment of MS.

Source of funding
Funded by Teva Neuroscience Inc.

Bibliographic details

PubMedID
17407391
Other publications of related interest
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Indexing Status
Subject indexing assigned by NLM

MeSH
Cost-Benefit Analysis; Drug Costs; Glatiramer Acetate; Health Care Costs; Humans; Immunologic Factors /economics /therapeutic use; Interferon beta-1a; Interferon beta-1b; Interferon-beta /economics /therapeutic use; Markov Chains; Models, Econometric; Multiple Sclerosis, Relapsing-Remitting /drug therapy /economics; Outcome Assessment (Health Care); Peptides /economics /therapeutic use; Quality-Adjusted Life Years; Research Design; Sensitivity and Specificity; Time Factors; Treatment Outcome; United States

AccessionNumber
22007001208

Date bibliographic record published
31/12/2007

Date abstract record published
31/12/2007