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COST-UTILITY ANALYSIS OF INTERFERON BETA-1B IN SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS

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Abstract

Objectives: Interferon beta-1b has recently become available for the treatment of secondary progressive multiple sclerosis (SPMS). This study aims at estimating the cost-effectiveness of this new treatment that has been shown in a clinical trial to reduce the progression of the disease. Effectiveness is measured as the number of quality-adjusted life-years (QALYs) gained from the reduction in progression. Because the clinical trial period will only capture part of the treatment's effect in terms of QALYs gained, since benefits achieved during the trial will have an effect beyond it, the cost-effectiveness analysis involves modeling over the longer term using complementary data.
Methods: A Markov model with states based on disability expressed by EDSS scores was used. Transition probabilities were calculated directly from clinical trial data for the first 3 years and then extrapolated to 10 years. Mean costs and utilities for each Markov state were calculated from a population-based cross-sectional study in Sweden.
Results: The incremental cost per QALY is SEK 342,700 (US $39,250; US $1 = SEK 8.73, March 10, 2000) when all costs (direct, informal care, and indirect) are included (discounted 3%). When indirect costs are excluded, the cost per QALY is SEK 542,000 ($62,100).
Conclusions: Cost-effectiveness analysis in SPMS requires that the effect of treatment beyond clinical trials be included. Also, analysis should be done from a societal perspective, since many of the costs occur outside the healthcare system. The cost-utility ratios estimated in this analysis are at or below the mean threshold value indicated in a recent survey of health economists ($60,000).

Keywords: Cost-utility, Secondary progressive MS, Modeling, Interferon beta-1b

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Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system white matter that affects young and middle-aged adults. It is the second most common cause of neurological disability in this age group (12). The onset of the disease normally takes place between 20–40 years of age, and women are affected about twice as often as men are. At onset, about 80% of the patients develop relapsing-remitting multiple sclerosis (RRMS) (22), and a majority of these patients will later develop secondary progressive multiple sclerosis (SPMS). The most common symptoms include spasticity, motor and sensory impairment, ataxia, tremor, vision changes, bowel, bladder, and sexual dysfunction, and fatigue. Functional disability is a major problem for patients early in the course of the disease, and the mean time to requiring an aid for ambulation is 15 years (33). However, the course of the disease for a specific patient cannot be predicted. The effect on mortality is minimal, and survival after onset in high-risk areas is in the order of 35 to 40 years (3).

The disease has a high social cost because it severely affects people's functioning early in life, with long survival after onset. Cost of care is high, with indirect costs representing a large component of the total burden. Henriksson et al. (13) have estimated the mean total cost per patient in Sweden for 1998 at 442,500 Swedish kronors (SEK) (US $50,700). When cost for interferon treatment is excluded, indirect costs represent approximately 40%. Other authors have found a higher share of indirect costs, partly due to a different distribution of costs between direct and indirect costs, and partly because nonmedical direct costs were rarely included (2;4;14;15;21;23;26).

Interferon beta-1b (IFNβ-1b) has been licensed in Europe for RRMS since 1995. In 1999 it was approved for the additional indication of SPMS in the 15 European Union member states, Switzerland, and Canada, based on a European clinical trial in 718 patients with SPMS treated with either IFNβ-1b or placebo for up to 3 years (9). The trial showed a significant positive effect of IFNβ-1b on the number of relapses and disease progression measured by the Expanded Disability Status Scale (EDSS), compared with placebo. It can thus be expected that the quality of life of patients will be improved and some of the management costs related to MS reduced through treatment with IFNβ-1b.

However, a 3-year trial in a chronic progressive disease such as MS will show only a partial effectiveness, since any benefit achieved during the trial will have an effect over the longer term. Any improvements in either disability or quality of life compared with placebo at the end of the trial will not be lost immediately, but may only gradually vanish over time if treatment is stopped. A delay in progression at the end of the trial will carry over into the future, even if progression continues. It is thus necessary to use modeling techniques to calculate the cost-effectiveness or cost-utility of treatments that affect disease progression, combining data from different sources (epidemiological, clinical, and observational data). Figure 1 illustrates graphically the effect of treatment on disease progression. Disease progression is most often expressed as increasing functional disability measured with the EDSS (18), and several studies have shown a relationship between functional disability and quality of life or utilities (5;6;23;28;32). Different disability levels can thus be associated with utilities and the health outcome expressed as quality-adjusted life-years (QALYs).

As MS affects a large number of different physical and social functions, QALYs are the only outcome measure that can incorporate all impacts of the disease and its treatments on disability and quality of life over a given time span. Other measures that have been used for the assessment of treatments in MS, such as numbers needed to treat to avoid one defined event (e.g., becoming wheelchair-bound or bedridden), will only capture a small part of the effects of the disease and/or its treatment. In chronic diseases, where quality of life may be one of the most important aspects, it is difficult to define one single appropriate endpoint, and the benefit of an intervention is the "area under the curves" rather than the avoidance of a defined event. QALYs incorporate both the quality and the quantity of life and are thus the most appropriate outcome measure for economic evaluation in MS.

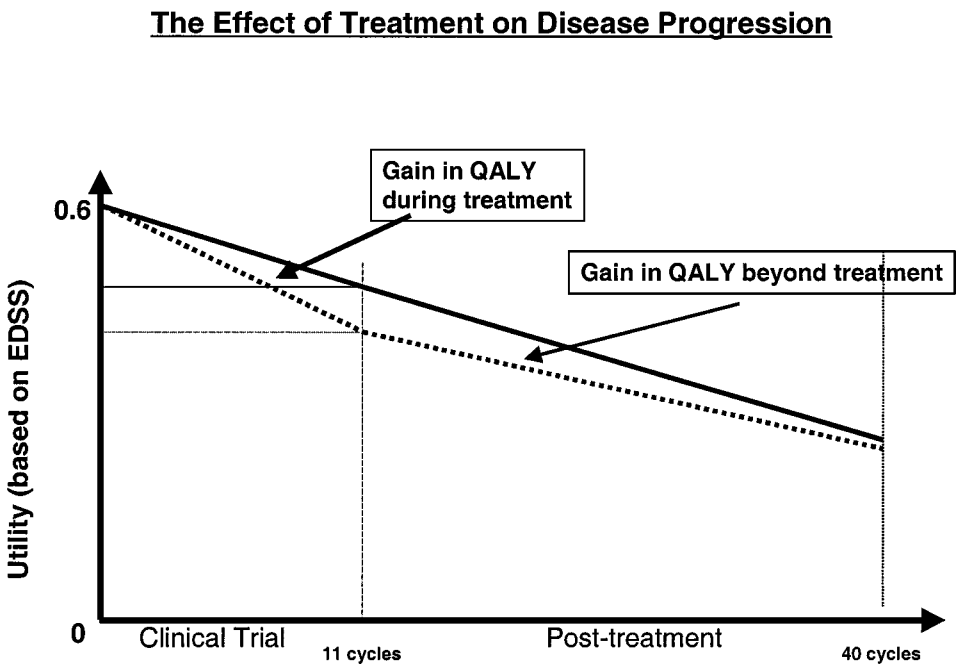

Figure 1. Illustration of the gain in QALYs during and after the clinical trial. The relationship between disability levels measured with EDSS and utilities has been shown in several studies. Thus, when disease progression is expressed as utilities, QALYs can be calculated. The areas between the curve illustrate the difference in QALYs between two hypothetical patient groups with or without treatment.

To estimate the cost-effectiveness of treatment of SPMS with IFNβ-1b, we developed a Markov model based on the clinical trial, complemented with data from a population-based observational study in Sweden (13). The model is based on an earlier model developed for the United Kingdom with the clinical trial data and cost and utility data from the literature (16). This original model has been modified for the present analysis, replacing the literature-based resource utilization information and utility measurements with new detailed data from the Swedish cross-sectional study.

This study estimates the incremental cost per QALY for treatment with IFNβ-1b compared with no treatment, from the point of view of society as the main perspective, in Sweden.

METHODS

The Model

When a decision problem involves risk that is persistent over time, Markov models are the most appropriate modeling technique (31). Markov models classify patients into a finite number of states, generally defined by the severity of the disease. Development of the disease is represented as transitions from one state to another, usually as progression to more severe states. The time horizon in Markov models is divided into equal increments of time, referred to as Markov cycles, and the length of the cycles is chosen to represent a clinically meaningful time interval. Spending one cycle in a particular state is associated with a certain cost and utility, and cumulative costs and utilities for the duration of the model are calculated. Since costs or benefits occurring immediately are valued more highly

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Table 1. Definition of Markov States Used in the Model

Markov state	EDSS scores
1	≤3.0
2	3.5, 4.0
3	4.5, 5.0
4	5.5, 6.0
5	6.5
6	7.0
7	>7.0
8	Dead

than those occurring in the future, discounting is performed to calculate present values of cumulative costs and utilities (17).

The basic MS model runs for 10 years in cycles of 3 months. Markov states are defined based on functional disability measured with the EDSS (18). The model uses seven disease states and one state for death. Using the EDSS, the difference between the states is small but was considered clinically relevant, as evidenced by the use of a one-point change in the EDSS as the primary clinical efficacy measure in the clinical trial. Larger groupings of EDSS levels, as used in earlier studies of the relationship between EDSS, quality of life, and costs (4;6;23;28;32), would not capture smaller changes in EDSS during the clinical trial and thus potentially underestimate the benefit of treatment. Table 1 indicates the groupings of EDSS levels.

Disease progression was calculated from the clinical trial with IFNβ-1b. Since no other disease-modifying treatment is currently approved for use in SPMS, the placebo group from the trial was used as the relevant clinical comparator in this analysis.

Transition probabilities for the first 11 cycles are based on changes in the EDSS in the clinical trial. Probabilities were calculated separately for patients with and without relapses, in order to also integrate the effect of IFNβ-1b on relapses into the model. The mean transition probabilities of the placebo cohort over the first 11 cycles were used to extrapolate to the period beyond the clinical trial to 40 cycles for both groups.

Although MS has some effect on mortality, there are not enough data to estimate the effect of treatment on mortality. The model thus only incorporates normal mortality in both arms, and no gains in survival from treatment or reduced progression of the disease is included in the analysis.

The basic structure of the model is illustrated in Figure 2.

Resource Utilization, Costs, and Utilities

Mean costs and utilities for each state were calculated from the observational study in Sweden (13). This study used a cross-sectional approach, where resource utilization and quality-of-life data and EDSS values were collected at a single time point. The study was performed by the Department of Neurology at Huddinge Hospital in Stockholm, and all patients with a confirmed diagnosis registered in the medical records at the Department of Neurology were included in the search. The search identified 615 patients, but 56 patients were excluded because they participated in another study, while 25 patients were either dead or could no longer be located. The final number of patients selected for the study was 543. Primary data were collected with an MS-specific patient questionnaire mailed to all patients selected. A total of 413 patients returned the questionnaire, a response rate of 76%.

The resource utilization questionnaire collected information on hospitalization, medical, and other visits (visits to physicians, nurses, and to rehabilitation centers as well as to paramedical practitioners), prescription and nonprescription drug usage, community and

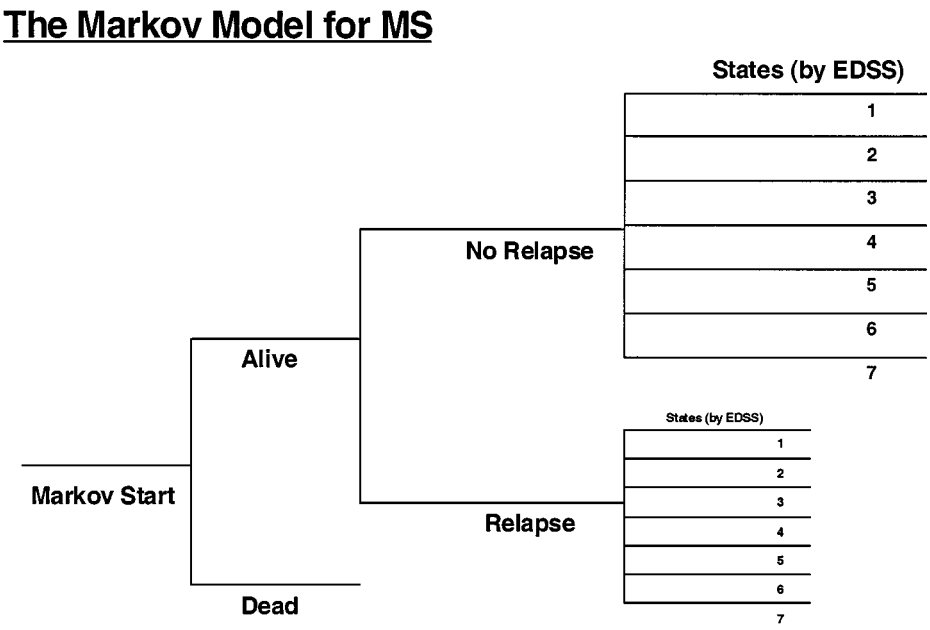

Figure 2. The structure of the Markov model. At each cycle, the model separates the cohort into dead/alive; living patients then move to the seven disease states separately, whether or not they have a relapse in that cycle.

other services, adaptations of the home or the workplace, medical and other devices purchased, and employment status. Resource utilization data covered a 1-month period prior to data collection for all resources, except for adaptations to the house or workplace and large investments (e.g., wheelchair), which covered a period of 1-year.

The reliability of patients' answers was verified by comparison to their hospital charts. Information on disease severity (EDSS scores) was taken directly from the medical records at the Department of Neurology. EDSS scores covered the full range from 0 to 9.5, and the mean EDSS score of the cohort was 4.93 (SD 2.52).

Unit costs for the resources were obtained from published sources, such as the Federation of County Councils (19;20), hospital price lists (1;30), the pharmaceutical lexicon (10), and through personal communication. Resources were multiplied with unit costs and grouped into direct and indirect costs. Direct costs included detection, treatment, rehabilitation, and long-term care. Informal care was also considered a direct cost but calculated separately. Indirect costs included short- and long-term absence from work and early retirement; premature mortality was excluded, since its impact in MS is small. Table 2 presents the mean annual cost per patient in the study.

Patients also completed the EuroQol (EQ-5D) (8). The EQ-5D provides a measure of overall health-related quality of life based on five descriptive questions with three levels of answers and a rating scale. Utility values between 0 (death) and 1 (full health) for the different combinations of possible answers in the descriptive part have been established in the general population in the United Kingdom using the time trade-off method. We used these values to calculate utilities for each patient from his or her answers to the EQ-5D, since similar normative values for Sweden are not yet available. As for EDSS scores, utilities covered almost the full range from negative utilities to 0.919, with the mean utility for the cohort being 0.42 (SD 0.39). With the EQ-5D, negative values are interpreted as a health state worse than death, but it is common to set negative utilities to zero.

Table 2. Cost Due to MS per Patient and Year (1998, Swedish Kronor)

Costs	Per patient and year (SEK)	Share of total costs (%)
Hospital inpatient care	21,097	4.8
Rehabilitation	37,950	8.6
Ambulatory care	33,119	7.5
Physicians	6,609	1.5
Nurses	9,380	2.1
Paramedical practitioners	17,130	3.9
Drugs (including interferons)	48,446	10.9
Services	98,806	22.3
Adaptations and devices	36,813	8.3
Informal care	20,668	4.7
Total direct costs	296,889	67.1
Short-term sickness absence	7,885	1.8
Long-term sickness absence and early retirement	137,692	31.1
Total indirect costs	145,577	32.9
Total cost	442,476	100.0

Costs and Utilities by EDSS Level

Patients from this cohort were grouped into the seven Markov states according to their EDSS score and the mean cost calculated for each state. These calculations excluded the cost of interferons and all costs related to a relapse, since these are calculated separately in the model. The mean direct cost of a relapse was estimated by comparing resource utilization incurred by patients with and without a relapse at the time of data collection, and the difference was considered to be due to the relapse. The direct cost of a relapse was estimated at SEK 16,800 (US $1,924), the mean total cost at SEK 25,700 (US $2,944).

The mean utility for each state was calculated using the descriptive part of the EQ-5D. The values obtained were very similar to published values for the middle ranges of EDSS used in the previous model (16), but were lower in the very mild and very severe states. This difference could be explained by the fact that the published studies covered mainly patients in the middle range of EDSS, and utilities for the very high and very low EDSS scores were obtained by regression analysis. The mean utility obtained in this cohort for the very severe state was negative (−0.027). Although the EQ-5D accepts that utilities can be negative for states considered worse than death, we set the utility for state 7 to zero for the main analysis, and present a sensitivity analysis for a utility of 0.10. The loss of utility during a relapse was calculated by comparing the utilities of patients in relapse with those of patients in remission and resulted in a 0.02117 for a 1-month relapse.

Table 3 presents the number of patients used for calculations in each state, the mean cost per cycle and patient, and the average utility for each Markov state.

The Cost of Treatment

The cost of treatment with IFNβ-1b was calculated using the official price list (10) and compliance in the clinical trial. The annual cost of SEK 110,900 (US $12,700) is divided by four to obtain the cycle cost. However, as the treatment effect in the model is based on the intent to treat (ITT) analysis of the clinical trial, including patients who had withdrawn from treatment but were followed up to the end of the trial, the treatment cost was adjusted to reflect actual usage in the trial. We multiplied the cycle cost with the proportion of patients who actually took the treatment during each 3-month period in the clinical trial and calculated the mean treatment cost per cycle. The average compliance in the trial was around 90%.

Table 3. Costs per Patient (3 Months) and Utilities for Different Markov States

State	Patients[a]	Utility	Mean 3-month costs in different states (SEK)			
			Direct costs	Informal care	Indirect costs	Total costs
1	124	0.677	8,957	126	20,109	29,192
2	36	0.534	19,566	3,611	30,312	53,489
3	26	0.544	27,991	2,675	28,508	59,174
4	59	0.496	26,511	1,509	34,746	62,766
5	54	0.333	75,871	8,330	46,745	130,946
6	21	0.210	97,697	5,417	39,746	142,860
7	87	−0.027[b]	149,942	14,352	56,696	220,990
Relapse		Utility loss				
	40	0.0635	18,528			27,612

US $1.00 = SEK 8.73.
[a] EDSS values were missing for six patients, and these were excluded from this analysis.
[b] Although the EQ-5D accepts negative utility values as plausible, the utility in state 7 was set to 0, and sensitivity analysis presented for a utility of 0.05 and 0.10.

It is likely that patients treated with interferons are monitored more closely. We compared the total cost of visits to physicians and nurses in the observational study between patients receiving interferons and those who did not and found a difference of around SEK 400 (US $46) per cycle. We considered this to be the extra management cost for IFNβ-1b and added it to the cost of treatment.

Cost-effectiveness

The main cost-effectiveness analysis is performed for a treatment intervention lasting 11 cycles, as in the clinical trial, compared with no intervention. Beyond the clinical trial, no further treatment effect is assumed, but the effect on progression during the first 11 cycles is carried forward to 40 cycles. The analysis is presented from the societal perspective and thus includes all costs. Both costs and utilities are discounted with 3%. Sensitivity analysis is presented for different perspectives, time horizons, discount rates, and utilities.

RESULTS

Figure 3 compares the cohort distributions after 11 cycles in the intervention and placebo groups. As can be seen, fewer patients go to the severe state 7 in the intervention group, while state 8 (dead) is identical in both groups. The distribution at 11 cycles matches exactly the distribution seen in the clinical trial. As no further effect is included after the end of the trial, the cohorts will converge after 10 years.

The effectiveness of the treatment, expressed as QALYs gained, is represented by the difference between the areas under the utility curves for the intervention and placebo groups, as illustrated in Figure 4.

In the base case the incremental QALY gain with treatment is 0.162 over 10 years for an incremental cost of SEK 55,500 (US $6,300), giving a cost per QALY of SEK 342,700 (US $39,250). When direct costs only are considered, savings in costs with treatment are SEK 155,200 (US $17,800), of which SEK 6,600 (US $756) are due to relapses avoided, while the remainder is due to progression avoided. When all costs are considered (excluding the cost of IFNβ-1b), savings are SEK 202,500 (US $23,200) and SEK 9,900 (US $1,134), respectively. Table 4 gives the results of the main cost-utility analyses.

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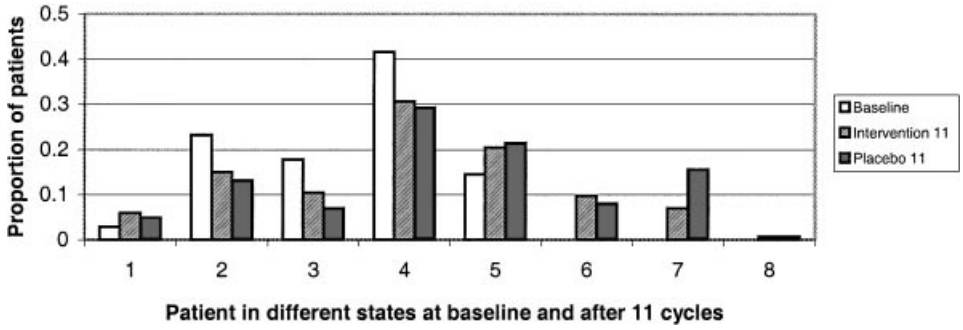

Figure 3. Cohort distribution after 11 cycles. The model starts using the baseline distribution of the entire cohort. Patients were predominantly in states 2–4, according to the enrollment criteria. Patients then move according to different transition probabilities in the treatment and placebo groups, and the cohort distribution after 11 cycles is shown.

Sensitivity Analysis

We also present the analysis with a time horizon corresponding to the clinical trial (11 cycles) and another of 5 years' duration. Both these scenarios will, however, ignore any carryover of the effect achieved during the trial, which will underestimate the benefit of treatment, as evidenced by the lower QALY gain (0.071 and 0.127, respectively). This compares to 0.162 in the base case, achieved without any further treatment effect after the trial. In addition, we estimated the cost-effectiveness for a discount rate of 5% (which is the rate suggested in most guidelines for economic evaluation), for a different utility in the

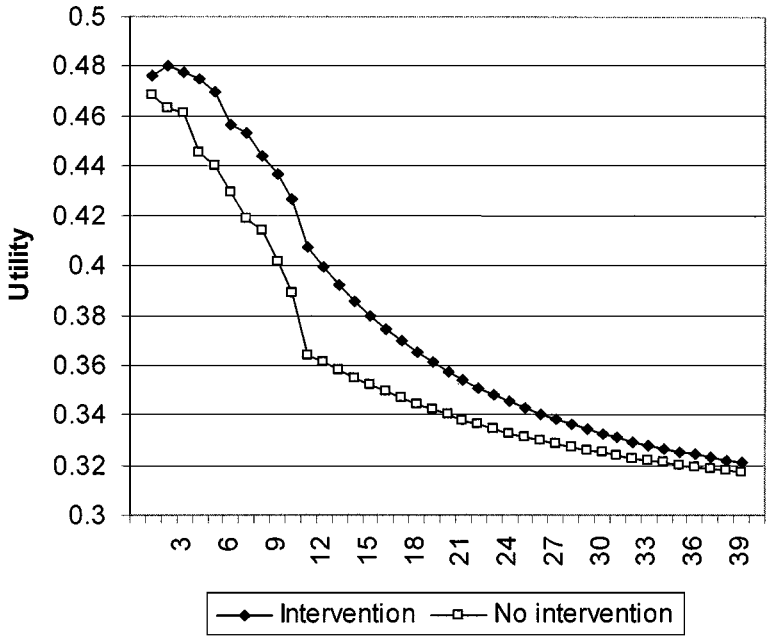

Figure 4. Expected utilities per cycle for the two groups over 10 years (undiscounted). The two curves indicate the expected mean utility per cycle of the two groups. The area between the two curves illustrates the QALY gain during the treatment and the carryover effect during the extension to 10 years.

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Table 4. Cost-Utility Analysis (10 years), Base Case

	Cost		Effect		Cost utility		
	Cost SEK	Increm. Cost SEK	Effectiveness QALY	Increm. Effect. QALY	Average CU SEK per QALY	Incremental CU SEK per QALY	Incremental CU $ per QALY
All costs included							
No intervention	3,724,400		3.153		1,181,241		
Intervention	3,789,900	55,500	3.315	0.162	1,140,266	342,700	39,250
Indirect costs excluded							
No intervention	2,358,500		3.153		748,034		
Intervention	2,446,300	87,800	3.315	0.162	737,967	542,000	62,100
Informal costs excluded							
No intervention	3,514,300		3.153		1,114,592		
Intervention	3,584,800	70,500	3.315	0.162	1,081,397	435,300	49,850
Direct costs only							
No intervention	2,148,400		3.153		681,384		
Intervention	2,251,200	102,800	3.315	0.162	679,097	634,600	72,200

US $1.00 = SEK 8.73.

Table 5. Sensitivity Analyses

Parameter changed compared to base case	Perspective	Cost per QALY (SEK)	Cost per QALY (US $)
Time horizon			
Time horizon 5 years	Societal	778,600	89,200
Time horizon 11 cycles	Societal	2,373,650	271,900
Utilities			
Utility in state 7 = 0.10	Societal	391,350	44,800
Relapse lasting 3 months	Societal	313,500	35,900
	Direct + informal costs	495,800	56,800
Relapse lasting 2 months	Societal	327,400	60,200
	Direct + informal costs	517,820	37,500
Discount rate			
5%	Societal	408,150	46,750
Management costs			
No extra costs for IFNβ-1b	Societal	320,100	36,650

US $1.00 = SEK 8.73.

most severe state (0.10) and different utility losses if relapses last 2 or 3 rather than 1 month, and for exclusion of the extra monitoring cost of IFNβ-1b. Table 5 presents these results.

DISCUSSION

This study presents a Markov model that allows estimating the cost-effectiveness of treatment with IFNβ-1b in patients with SPMS. The model is based on the only major clinical trial available at the time of this analysis, comparing IFNβ-1b to placebo in patients with SPSM over 3 years. The model incorporates the effectiveness of treatment based on the development of EDSS scores in the two groups, but other sources have been used to calculate mean costs and utilities in the Markov states. This is standard practice, since resource utilization in clinical trials is protocol-driven and may therefore differ considerably from clinical practice. Also, it is difficult in multinational trials to collect detailed data on nonmedical and indirect costs, as well as on informal care. A further limitation of clinical trials in MS for use in modeling is that patients with severe disease (e.g., EDSS 6.5 and above) will not be included. While some patients may progress toward severe states during the trial, their numbers may be too small to reasonably estimate mean costs and utilities at these levels. This might be less of a problem when disease levels are expressed as mild, moderate, and severe, as has been done in all economic studies in MS so far. However, it is insufficient in a model such as the one presented here, where disease states are defined by a one-point difference in EDSS to allow the model to pick up small changes in EDSS seen over a relatively short period of time.

We therefore calculated costs and utilities by state from a large cross-sectional study in which the entire spectrum of disability as expressed by EDSS scores was represented. The study included patients with different types of MS, and a considerable number of patients with RRMS were receiving interferons. One solution would therefore have been to include only patients with SPMS in our calculations, accepting that the number of patients per state would be reduced. However, a comparison of total costs per patient and state (excluding the cost of interferons) between the types of MS revealed no difference. Similarly, a comparison of total costs per patient with RRMS treated or not treated with interferons did not show any difference in any of the states (excluding again the cost of interferons and the special monitoring costs). This confirms that EDSS is a very good predictor of costs for MS patients, even when patients at certain levels of EDSS can have different courses of the disease. We

therefore included all patients in the observational study in our calculations of costs and utilities by EDSS level.

The observational study was performed in the county of Stockholm. With the exception of the fact that more patients with RRMS may have received interferons than in the rest of Sweden, there is no indication that patients in the Stockholm area are different. This is confirmed by the fact that costs by EDSS level did not differ between treated and untreated patients. While the distribution of the cohort over the range of EDSS may have been affected, this is not relevant for our model, since only the costs and utilities by EDSS level from this study are included, with no data on progression.

Utilities in the low and high ranges of EDSS were found to be lower in the Swedish study than in other published reports. This is likely due to the fact that most studies included no or very few patients in these ranges, particularly the very severe levels, while the Swedish study included 108 patients at EDSS levels 7.0 and above. Thus, our values can be considered the most accurate available to date.

In our model, patients stop treatment with IFNβ-1b according to the compliance in the clinical trial, and all patients stop after 11 cycles. While this may be somewhat of an artificial situation, as in clinical practice, patients in whom treatment appears effective would remain on treatment beyond the trial. However, no data are available yet on the effectiveness beyond the trial, and any extension would involve assumptions based on the effect within the trial. Similarly, compliance beyond the clinical trial is not known and assumptions would have to be made. This would affect both the effectiveness and the cost of treatment. We therefore chose to only include treatment effects and costs that are known, but carry the effects on EDSS and utility and the cost savings in the cost of care forward.

The natural course of the disease was extrapolated from the placebo group in this model. Patients included in the trial were a somewhat selected group with very active disease, and this may affect our estimates of disease progression beyond the trial. However, these patients represent the group that would be treated with IFNβ-1b, and the extrapolation can therefore be considered relevant. In a next step, the model will be revised to include natural history data for the extension.

Most previous cost-effectiveness analyses have used the published clinical data with IFNβ-1b in RRMS, extrapolating them to SPMS. Recently, analyses for the United Kingdom using the published clinical data in SPMS have been reported (11;25;27). Our results differ from these studies, partly due to the fact that the model is based on the raw clinical data on EDSS changes and relapses rather than on aggregate reports. Also, our study includes outcomes achieved at all levels of the disease, while these authors focus on reaching a certain level of disability (need of a wheelchair) and thus ignore benefits to the patients occurring before and after becoming wheelchair-bound.

Policy Implications

The cost-effectiveness ratios are at the higher end of the range found in studies in other diseases in Sweden. Cost-effectiveness ratios up to US $30,000 have been accepted as cost-effective in previous studies (29). The questions of what is an acceptable cost-effectiveness ratio or what the willingness to pay for a QALY is have not been fully answered. Johannesson has used benchmark values of US $40,000, 60,000, and 100,000 per QALY gained (submitted for publication). The middle threshold value of US $60,000 was used as the main alternative and corresponds to the mean value indicated as the value to be used in cost-effectiveness analysis in a recent survey of health economists (24). The highest value was used as a value per QALY gained in a study of the value of increased health of the U.S. population over time (7). Our overall results fall within this range, but the important decision will be which patients should be treated when and for how long.

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