Multiple Sclerosis 2005; **11:** 542–551
www.multiplesclerosisjournal.com

Economic evaluation of Avonex® (interferon beta-1a) in patients following a single demyelinating event

Michael Iskedjian[*,1], *John H Walker*[1,2], *Trevor Gray*[3], *Colin Vicente*[1], *Thomas R Einarson*[1,4] *and Adel Gehshan*[5]

[1]*PharmIdeas Research and Consulting Inc., Oakville, Ontario, Canada;* [2]*Faculty of Business, Brock University, St. Catharines, Ontario, Canada;* [3]*St. Michael's Hospital, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada;* [4]*Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada;* [5]*Biogen Idec Canada Inc., Mississauga, Ontario, Canada*

Background: *Interferon beta-1a (Avonex®) 30 μg, intramuscular (i.m.), once weekly is efficacious in delaying clinically definite multiple sclerosis (CDMS) following a single demyelinating event (SDE). This study determined the cost effectiveness of Avonex® compared to current treatment in delaying the onset of CDMS.* ***Methods:*** *A cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) were performed from Ministry of Health (MoH) and societal perspectives. For CEA, the outcome of interest was time spent in the pre-CDMS state, termed monosymptomatic life years (MLY) gained. For CUA, the outcome was quality-adjusted monosymptomatic life years (QAMLY) gained. A Markov model was developed with transitional probabilities and utilities derived from the literature. Costs were reported in 2002 Canadian dollars. Costs and outcomes were discounted at 5%. The time horizon was 12 years for the CEA, and 15 years for the CUA. All uncertainties were tested via univariate and multivariate sensitivity analyses.* ***Results:*** *In the CEA, the incremental cost of Avonex® per MLY gained was $53 110 and $44 789 from MoH and societal perspectives, respectively. In the CUA, the incremental cost of Avonex® per QAMLY gained was $227 586 and $189 286 from MoH and societal perspectives, respectively. Both models were sensitive to the probability of progressing to CDMS and the analytical time horizon. The CUA was sensitive to the utilities value.* ***Conclusion:*** *Avonex® may be considered as a reasonably cost-effective approach to treatment of patients experiencing an SDE. In addition, the overall incremental cost-effectiveness profile of Avonex® improves if treatment is initiated in pre-CDMS rather than waiting until CDMS.*

Multiple Sclerosis (2005) ***11,*** *542–551*

Key words: *Canada; cost effectiveness; economic; interferon beta-1a; multiple sclerosis; single demyelinating event*

Background

Multiple sclerosis (MS) is a chronic neurological disease with serious long-term consequences. Diagnosis of clinically definite multiple sclerosis (CDMS) requires that a patient experience at least two neurological demyelinating events separated in both time and space.[1,2] A single demyelinating event (SDE) has been defined as a neurologic event consistent with demyelination, which may be identified through the use of magnetic resonance imaging (MRI).[3,4] As reported, 'the presence of such MRI-identified lesions in a patient with an isolated syndrome of the optic nerve, spinal cord, or brain stem or cerebellum of recent onset is associated with a high risk of clinically definite multiple sclerosis [CDMS]'.[3,5–7]

A recent study by Jacobs and colleagues reported that interferon beta-1a (Avonex®), when used as treatment following an SDE, is efficacious in delaying the progression into CDMS.[3] By delaying progression, Avonex® may have the potential to reduce the burden of illness and increase the quality of life in patients after an SDE. That study reported that the cumulative probability of developing CDMS was significantly lower in the Avonex® group compared to placebo (rate ratio 0.56; $CI_{95\%}$ 0.38–0.81; $P = 0.002$). The same study determined the median time to CDMS to be three years for the placebo group compared to five years for those receiving Avonex® treatment.[3]

Once a patient is diagnosed with CDMS, progression is determined through the use of the Expanded Disability Status Scale (EDSS).[8] Numerous studies have reported that the cost of treating and caring for MS patients increases with EDSS level.[9–13] In addition, patients have reportedly experienced a clinically diminished quality of life as the progression of MS continues into more severe EDSS levels.[10,11,13,14] Thus, treating patients with Avonex® following an SDE may provide long-term benefits by delaying the progression to CDMS, and delaying the associated progression of disability and diminishing effects on quality of life. This profound effect may provide additional quality adjusted life years (QALY) to patients treated with Avonex®.

Few studies have looked at the cost-effectiveness or cost-utility of interferon beta-1a for treatment in MS.

**Correspondence: Michael Iskedjian, PharmIdeas Research and Consulting Inc., 1175 North Service Road West, Suite 211, Oakville, Ontario, Canada L6M 2W1.*
E-mail: skedji@pharmideas.com
Received 25 May 2004; accepted 1 April 2005

10.1191/1352458505ms1211oa

A study performed in the UK by Parkin and colleagues reported the incremental cost per QALY gained in patients with relapsing–remitting MS. The comparators in that analysis were interferon beta-1b and standard management. They reported an incremental cost per QALY gained of £328 300 over a five-year period and £228 300 over a ten-year period.[15] No study has been reported on the cost-effectiveness of Avonex® when used as treatment following an SDE.

We performed a pharmacoeconomic analysis of Avonex® compared to current treatment in patients who have experienced an SDE. Our goals were as follows: i) to perform a cost-effectiveness analysis (CEA) of SDE treatment based on the additional monosymptomatic life years (MLYs) gained, and ii) to perform a cost-utility analysis (CUA) of long-term treatment comprising both monosymptomatic and CDMS phases, based on the additional QALYs gained with Avonex® treatment.

Methods

This study was performed in compliance with the guidelines put forth by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA).[16] Analyses were conducted from both the Ministry of Health (MoH) and societal perspectives (SOC).

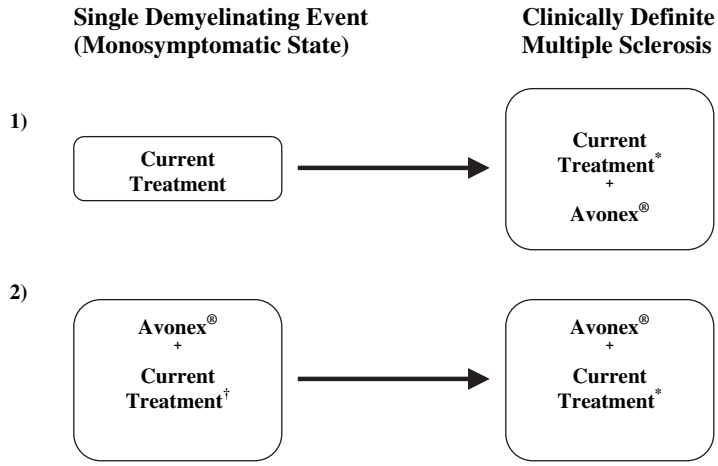
The target population for this indication of Avonex® included patients who had experienced a single, clinically diagnosed, demyelinating event and who were at risk of progressing to CDMS. The target population has been described elsewhere.[3]

A CEA was used to compare expected costs and outcomes. The primary outcome of interest was the duration of time between an SDE and entering into CDMS. This time frame was termed the monosymptomatic state. A CUA was used to evaluate long-term treatment from the monosymptomatic state, following an SDE, through all of the stages of CDMS. Two analytic models were developed, one for the CEA and one for the CUA. Both models were flexible to account for either the monosymptomatic stage on its own or both the monosymptomatic and CDMS stages. Each model incorporated data from the literature and clinical expert opinion in evaluating their respective outcomes. The model comprised two treatment arms in the monosymptomatic state which were Avonex® and Current Treatment [intravenous (i.v.) methylprednisolone]. Avonex® was administered as 30 μg intramuscular (i.m.) injections once weekly, and methylprednisolone was given as four i.v. injections of 1 g for 3 days followed by 14 days of oral steroids 1 mg twice daily. Once in CDMS, all patients were treated with Avonex® and were provided i.v. methylprednisolone to treat symptoms related to a relapse. A graphical summary of treatment comparators is presented in Figure 1.

The analytical time horizon for the CEA was determined by doubling the projected median time to progress to CDMS for the Avonex® arm of approximately six years, using the Kaplan Meier estimates report by Jacobs *et al*.[3] As a result, by analysing over 12 years, we were able to capture the outcomes of treatment following an SDE for the majority of patients in our study.

The time horizon for the CUA was set at 15 years. The time horizon was determined after adding the median time to progress to CDMS (approximately six years), as in the CEA, to the median time to EDSS 3 (approximately seven years). A sensitivity analysis was performed at 20 and 30 years to assess the uncertainty in capturing all relevant outcomes at 15 years.

Data for progression to CDMS were derived from efficacy results reported by Jacobs and colleagues.[3] That study, also known as the CHAMPS study, was conducted as a randomized, multicentre, double-blind, placebo-controlled trial comparing patients receiving either 30 μg of Avonex® i.m. once weekly for three years or placebo. Prior



*Current treatment was incorporated into the treatment regimen at each relapse.

†Current treatment was incorporated into the treatment regimen at the time of an event.

Figure 1 *Summary of treatment options and transition states considered in the model.*

to study inclusion, all patients were treated with 1 g of methylprednisolone i.v. daily for three days, followed by 1 mg of prednisone per kg of body weight per day orally for 11 days. That was followed by a four-day period of tapering in which 20 mg was given on day 1, 10 mg on day 2, 0 mg on day 3 and 10 mg on day 4. All patients included in the study had experienced an SDE and were at risk for developing CDMS based on the presence of subclinical MRI visible lesions. The primary efficacy outcome was the diagnosis of CDMS. Jacobs and colleagues reported that Avonex® significantly reduced the progression to CDMS compared to placebo with a rate ratio of 0.56 ($CI_{95\%}$ 0.38–0.81; $P=0.002$).

Data for the progression through the various stages of CDMS were derived from a study by Weinshenker and colleagues.[17] That study followed 1099 MS patients evaluated in a Canadian MS clinic. Data from the majority of patients were collected retrospectively; however, 197 patients were followed prospectively from the onset of MS. Weinshenker reported on the clinical course of MS, including the median times to DSS 3 and DSS 6. The Weinshenker data applied to all patients with CDMS and did not report subgroup analyses of a patient sample similar to the population studied by Jacobs.

Two main treatment outcomes were 1) MLYs gained and 2) quality adjusted monosymptomatic life years (QAMLYs) gained. The time spent in pre-CDMS was captured as MLYs gained and then quality adjusted using utilities derived from the literature.

In the CEA, the primary goal was to quantify the time spent in the monosymptomatic state following an SDE, prior to progression to CDMS. Patients who remained in that state were assigned a MLY. That benefit was based on the assumption of a clinically superior state than states already advanced into CDMS (EDSS 1, EDSS 2, EDSS 3, EDSS 4, EDSS 5 and EDSS 6+). On the other hand, patients who progressed into CDMS received no benefit but continued to accrue the costs associated with their respective severity levels of CDMS.

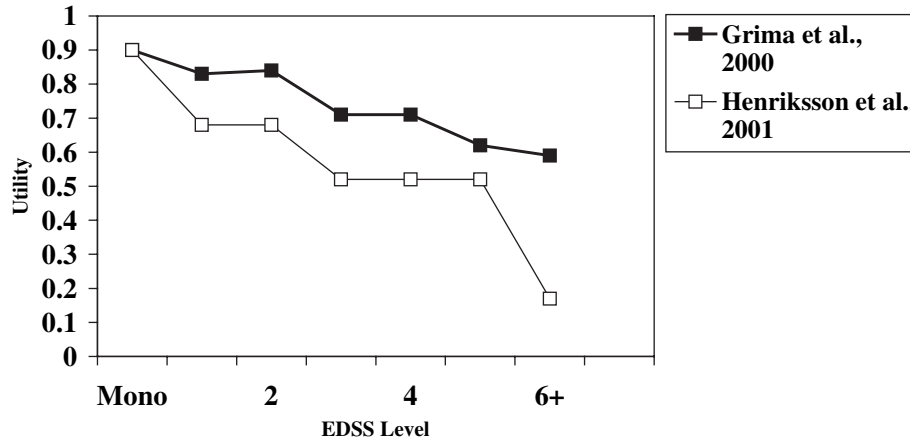
In the CUA, we estimated the long-term benefits of treating patients following an SDE and as they progressed through the various stages of CDMS. The outcome used to represent the effect was QAMLY gained. Utilities were applied to each health state, and the utility-adjusted time spent at each health state was determined, then summed across all states. The result was a quality weighted average time per patient.

The utilities for the CUA were derived from a study by Grima *et al*. which used the Health Utilities Index questionnaire (HUI).[10] The HUI values were based on data collected from Canadian MS patients; hence, the HUI values were used for our base case CUA. A regression analysis was performed to estimate the utility value for the monosymptomatic state, assuming, for analytic simplification, that progression would occur in a linear fashion. Available data were not sufficient to use more complex regression techniques.

A second utility based analysis was performed after discussions with clinical and pharmacoeconomic experts revealed that the HUI results might not represent the best estimate of utilities. The second analysis used utilities derived from an extensive quality of life study performed by Henriksson and colleagues in a Swedish patient cohort.[13] Henriksson reported utilities based on data derived from the use of the EQ-5D questionnaire (EuroQol).[18] The EuroQol derived utilities were used in a sensitivity analysis in the present analysis. All utilities applied in the analyses are depicted in Figure 2.

A 5% discount rate was applied to both costs and outcomes in our base case as suggested by the CCOHTA guidelines.[16] To test for the robustness of our two models to the discount rate, sensitivity analyses were performed varying it to 3% and 0%.

Costs were identified through a literature review restricted to those studies performed in a Canadian setting[9,10] and through discussions with a Canadian clinical expert. All resources, valued in 2001 Canadian dollars (CAD), are presented in Table 1. Unit costs were derived from various reference lists such as The Ontario Drug



*Grima et al.[10] applied the Health Utilities Index (HUI), while Henriksson et al.[13] used the EuroQol to measure patient utilities for various states in multiple sclerosis.

Figure 2 *Summary graphic representation of utilities.*

Table 1 Total expected costs ($) by severity level for Avonex® treatment in MS

Severity level	*Year of relapse*		*Year of remission*	
	MoH	*SOC*	*MoH*	*SOC*
Avonex®: monosymptomatic state*	20 171[†]	57 163[†]	18 833	30 050
Current treatment: monosymptomatic state*	1 513	38 505	175	11 392
Both treatment arms				
EDSS $\leq$3.5	20 254	55 063	18 916	28 595
EDSS 4–5.5	21 008	75 228	19 040	43 561
EDSS $\geq$6	30 543	103 036	19 248	52 557

*Indirect costs were estimated using the probability of progression to each EDSS level and the indirect cost associated with each level.
[†]Costs associated with the year of an event.
MoH, Ontario Ministry of Health analytic perspective; SOC, societal analytic perspective.

Benefits Formulary,[19] the Ontario Schedule of Benefits for Physician Fees and Services[20] and the Ontario Schedule of Benefits for Laboratory Services.[21] All costs were stratified by CDMS severity level: monosymptomatic state, mild (EDSS $\leq$3.5), moderate (EDSS 4–5.5) and severe (EDSS $\geq$6).

The average hospital length of stay (ALOS) within each EDSS level was determined by expert clinical opinion and was verified using data from the Ontario Case Costing Initiative (OCCI).[22] The OCCI was then used as a reference to value the cost of hospitalizations. The hospital costs per EDSS level were derived by determining the probability of hospitalization at each level and then by multiplying the specific probability by the cost value of hospitalization for that level. The probabilities were determined by expert clinical opinion.

Unemployment rates by EDSS level were reported by Grima *et al*.[10] That study did not include patients with an EDSS level >6; thus, we used clinical expert opinion to determine the effect of severe MS on the ability to be employed. The number of missed work-days were derived using data reported by the Canadian Burden of Illness Study.[14] Unemployment was then valued in CAD using a 40-h work week and an average hourly industrial wage of $16.50.[23]

The Human Capital Approach was used to value lost time due to MS. The value of lost time was equal to the benefit the patient would have accrued if the lost time had been used for its best alternative resource, i.e., income.[24] Thus, the cost of each hour of lost time was valued at the hourly rate of $16.50 as per the value of lost productivity due to unemployment. The value of lost time, as a result of missed workdays, was influenced by a factor equal to 1−(rate of unemployment). This factor was utilized to avoid double counting the lost time due to unemployment, i.e., unemployed patients could not miss workdays.

The value of lost time due to missed leisure hours was not influenced by employment status. Both employed and unemployed patients were assumed to have lost leisure hours. Lost leisure time was quantified using data reported by the Canadian Burden of Illness Study.[14]

Data were unavailable for the indirect costs associated with the monosymptomatic state. As a result, the authors included an approach that valued indirect costs at the monosymptomatic state as an average of the indirect costs at each EDSS level, weighted by the probability of moving from the monosymptomatic state to the specific EDSS level. This approach was verified through clinical expert opinion and tested in a sensitivity analysis.

Costs for the SOC perspective include all the direct medical costs as well as the costs associated with lost productivity due to MS, costs associated with caregivers to the MS patients and costs associated with nonworking time. It is important to distinguish between these two perspectives because the MOH perspective only deals with the outcomes and direct medical costs associated with these outcomes that are borne by the decision makers of a reimbursement programme. The societal perspective includes all outcomes and their associated costs regardless of who experiences the outcomes or incurs the costs. Total Costs were calculated from the MoH and SOC perspectives as follows:

$$\begin{aligned}\text{Total Cost MoH} &= \text{Medications} + \text{Pharmacist fees} \\ &\quad + \text{Medication administration fees} + \text{Physician fees} \\ &\quad + \text{Diagnostic procedures} + \text{Laboratory testing fees} \\ &\quad + \text{Hospitalization}\end{aligned}$$

$$\begin{aligned}\text{Total Cost SOC} &= \text{Total Cost MoH} \\ &\quad + \text{Lost Productivity (i.e., unemployment and days missed from work)} + \text{Caregiver Time Lost} \\ &\quad + \text{Leisure Time Lost.}\end{aligned}$$

Total costs were stratified by severity level and derived for each year of the model. The first year at each severity level included all costs associated with a relapse, while subsequent years reflected the costs derived while in remission. Summaries of the total costs by MS severity levels are presented in Table 1.

Two Markov models were developed. The models were applied to estimate the costs and outcomes of Avonex® treatment following an SDE: the first model captured outcomes until progression to CDMS; the second model also estimated the long-term costs and outcomes of progression through various severity levels associated with CDMS. A condensed version of our model is presented in Figure 3.

The length of each cycle was set as one year. The monosymptomatic health state was used as the entry

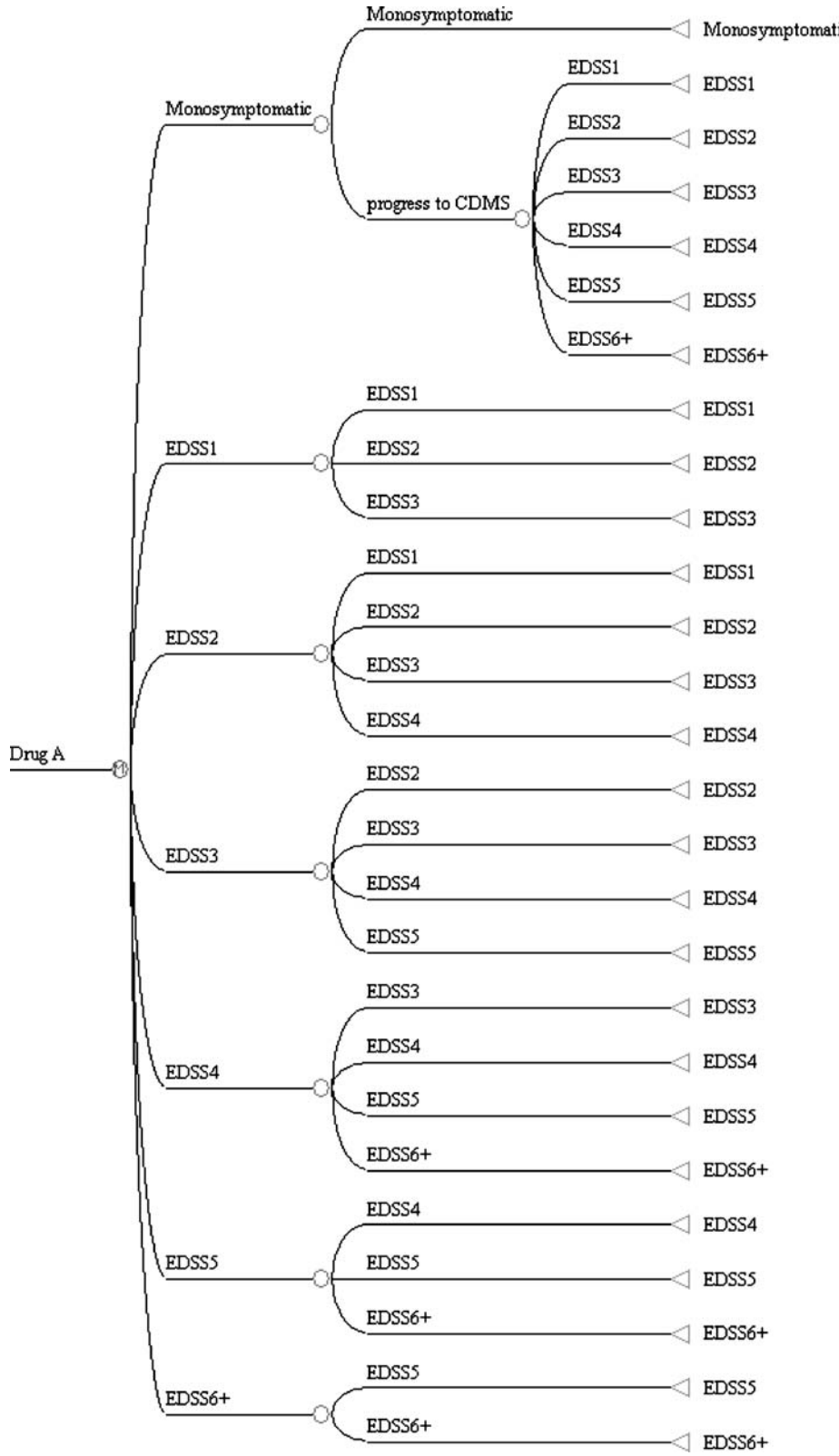


Figure 3 *Decision tree.*

point for all patients following an SDE; thus, the probability of being in the monosymptomatic health state during the first cycle is 1.0. At the end of the first year, patients could either stay monosymptomatic or experience an event and transition into CDMS at EDSS levels 1–6. The probability of transitioning out of the monosymptomatic state was derived using Kaplan–Meier estimates from the CHAMPS study as reported by Jacobs.[25]

Table 2 Summary of transitional probabilities from the monosymptomatic health state

Scenario	*Transitional probability (%)*		*Source*
	Current treatment	*Avonex®*	
Monosymptomatic to EDSS1	0.080 (38.6)	0.052 (38.6)	Jacobs *et al*.[25]
Monosymptomatic to EDSS2	0.063 (30.7)	0.041 (30.7)	Jacobs *et al*.[25]
Monosymptomatic to EDSS3	0.045 (21.9)	0.029 (21.9)	Jacobs *et al*.[25]
Monosymptomatic to EDSS4	0.004 (1.8)	0.002 (1.8)	Jacobs *et al*.[25]
Monosymptomatic to EDSS5	0.009 (4.4)	0.006 (4.4)	Jacobs *et al*.[25]
Monosymptomatic to EDSS6	0.005 (2.6)	0.003 (2.6)	Jacobs *et al*.[25]
Total	0.206 (100)	0.134 (100)	Jacobs *et al*.[25]

Table 2 contains the total probability of transitioning into the CDMS state and the associated probabilities of moving to each EDSS level from the monosymptomatic state.[25]

In the second cycle (i.e., Year 2), patients could again transition from monosymptomatic to EDSS. However, patients who started Year 2 in an EDSS level had their transitioning ability restricted to the same EDSS level, remission into one EDSS level below or relapse 1 or 2 EDSS levels above the current state. Patients in EDSS Level 1 could not transition back to the monosymptomatic state. This process repeated itself in a Markov model until the end of the time horizon.

The probabilities associated with transitioning through the various EDSS stages of the model were time dependent.[17] Tracker variables were used to account for the number of years spent at each CDMS level. As a result, the probability of transitioning was dependent on the tracker variable for that patient. All outcomes were determined using a 10 000-iteration Monte Carlo simulation. A Monte Carlo simulation was used so that the tracker variables could be referenced to determine the time spent at each EDSS level. Thus, the software could apply the appropriate time-dependent transitional probability in its calculations. The probabilities for transitioning through the various EDSS levels were derived from Weinshenker *et al*.[17] The CDMS transitional probabilities associated with both arms were equivalent. As a result, the delay into CDMS is expected to be a key factor in differentiating between the two treatment arms.

The following is a list of key assumptions used to develop our model and to deal with uncertainties:

- Patients in both treatment arms were treated with Avonex® once CDMS was diagnosed.
- Relapse rates were set to one per every two years.
- Relapses were assumed to last for two months.
- Both Avonex® and current treatment patient compliance was assumed to be 100%.
- The indirect costs of the monosymptomatic state were estimated based on the indirect cost of each EDSS level then weighted by the probability of transitioning from the monosymptomatic state to the respective EDSS level.
- Patients were restricted in their movement following a relapse.

Sensitivity analyses were performed to determine the robustness of our model, i.e., how sensitive the model was to alterations in key parameters, and to deal with uncertainties inherent to the parameters used in the model. The parameters to test were determined through discussions with the pharmacoeconomic and clinical experts in the investigative team. Key parameters to test were the progression rate to CDMS following an SDE and the indirect costs associated with the monosymptomatic state. Additional parameters tested in the sensitivity analyses included the analytical time horizon required to capture the relevant outcomes, the discount rate and the utilities.

Parameters were additionally tested in multivariate, Monte Carlo analyses using 10 000 iterations. For the Monte Carlo analyses, parameters such as the probability of progression to CDMS, the utilities and the indirect costs of the monosymptomatic state were varied, based on available data, using appropriate distributions as determined via discussions with clinical and pharmacoeconomic experts.[26]

Results

We calculated, from this model, that the median time for the Avonex® group to progress to CDMS was 5.8 years compared to 5 years as reported in the Jacobs study.[3] The criterion for the median times to progress to EDSS 3 and 6 are 7.7 and 14.9 years, respectively, as reported by Weinshenker.[17] The median times to progress to EDSS 3 and 6, in this model were 6.8 and 14.6 years, respectively. All predictive results were within approximately 15% of the reference criteria. Thus, the model provided a good estimation of the time to progress from an SDE to severe CDMS.

From the MoH perspective, the expected costs per patient over the time horizon of 12 years were $173 000 and $108 000 for Avonex® and current treatment, respectively. Expected MLYs were 4.69 and 3.48, respectively. As a result, the cost-effectiveness ratio for Avonex® was $36 811 per MLY gained and for current treatment was $31 144 per MLY gained. The incremental cost-effectiveness of Avonex® was $53 110 per MLY gained from the MoH. Results for the cost-effectiveness analyses are reported in Table 3.

From the SOC perspective, the expected costs per patient were $317 000 and $262 000 for Avonex® and current treatment, respectively, over 12 years. As a result, the cost-effectiveness ratio for Avonex® was $67 503 per

Table 3 Summary of base case and sensitivity analyses results for the cost-effectiveness model*

Parameter modified	*Parameter value*	*Incremental cost/MLY*	
		MoH	*SOC*
Base case	NA	$53 110	$44 789
Time horizon	6 years	$85 116	$79 335
Discount rate	0.00	$46 098	$37 382
	0.03	$50 243	$41 776
Probability of CDMS	+25%	$44 685	$35 567
	−25%	$67 828	$60 241
Indirect costs	+25%	NA	$42 709
	−25%	NA	$46 869
Mono indirect costs	0%	NA	$33 828
	−50%	NA	$37 037
Dose of oral prednisone	1 mg/day for 14 days	$50 692	$43 798

*The time horizon for the base case analysis was 12 years, and the discount rate was 5%.
MoH, Ministry of Health analytic perspective; Mono, monosymptomatic state; NA, not applicable; SOC, societal analytic perspective.

MLY gained and for current treatment was $75 444 per MLY gained. The incremental cost of Avonex® per MLY gained was $44 789. Since the incremental cost was lower than the average cost per MLY gained of current treatment, it was considered cost effective.

Results for the cost-utility analyses are reported in Table 4. In the base case analysis, outcomes were based on the HUI derived utilities. The incremental cost of Avonex® per QAMLY gained was $227 586 per QAMLY from the MoH perspective and $189 286 per QAMLY from the societal perspective. Performing the same CUA with the EuroQol resulted in an incremental cost per QAMLY gained of $116 071 and $91 228 for the MoH and SOC perspectives, respectively. Results for the EuroQol based CUA are reported in Table 4.

Table 4 Summary of the base case and sensitivity analyses results for the cost-utility model*

Parameter	*Sensitivity value*	*Incremental cost/QALY*†	
		MoH	*SOC*
Base case	NA	$227 586	$189 286
Time horizon	20 years	$183 333	$140 000
	30 years	$165 000	$117 949
Discount rate	0.00	$179 545	$132 550
	0.03	$212 121	$154 286
Utilities	EuroQol	$116 071	$91 228
	Average of HUI & EuroQol	$154 762	$126 191
Probability of CDMS	+25%	$186 207	$135 714
	−25%	$296 429	$244 828
Relapse rates	+25%	$216 667	$182 759
	−25%	$224 138	$192 857
Indirect costs	+25%	NA	$160 000
	−25%	NA	$183 333
Mono indirect costs	0%	NA	$127 266
	−50%	NA	$154 503
Utility lost on relapse	+50%	$216 667	$173 333
	−50%	$227 586	$189 286
Dose of oral prednisone	1 mg/day for 14 days	$227 131	$186 443

*The 15-year model was used in the base case analyses.
MoH, Ministry of Health analytic perspective; Mono, monosymptomatic state; NA, not applicable; SOC, societal analytic perspective.

Sensitivity analyses

The MLY model was sensitive to both the time horizon and the rate of progression into CDMS. A six-year time horizon resulted in an incremental cost per MLY gained of $85 116 and $79 335 for the MoH and SOC perspectives, respectively. Increasing the probability of progressing to CDMS reduced the incremental cost per MLY gained to $44 685 and $35 567 for the MoH and SOC perspectives respectively. Decreasing the probability of progression to CDMS resulted in an increase in the incremental cost per MLY gained, relative to the base case, of $67 828 for the MoH and $60 241 for the SOC perspective. This result was anticipated as decreasing the progression would narrow the relative difference in progression rates between the Avonex® and Current Treatment arms. An additional key sensitivity parameter was the indirect cost associated with the monosymptomatic state. When the indirect costs were varied to 50% and 0% of their base case value and incremental cost per MLY gained change to $37 037 and $33 828 respectively. Results for the sensitivity analyses are summarized in Table 3 for the CEA.

The QAMLY model was sensitive to variations in the utilities, time-horizon and probability of progression to CDMS. The utilities were tested using the EuroQol values in place of the HUI values. The incremental cost per QAMLY gained decreased to $116 071 for the MoH and $91 228 for the SOC perspectives. The sensitivity to the time horizon demonstrated the improved pharmacoeconomic profile of Avonex® when used as a long-term treatment. Results of the sensitivity analyses are summarized in Table 4 for the CUA.

Multivariate sensitivity analyses were performed on both models from both the MoH and SOC perspectives. Results of the multivariate analyses are summarized in Table 5. From the MoH perspective the median ICER was $50 029 per MLY gained and from the SOC perspective $43 566 per MLY gained. The median incremental cost per QAMLY gained in our multivariate analysis was $285 778 and $249 380 from the MoH and SOC perspectives, respectively.

The results of the multivariate analysis of the CEA have been presented as scatter plots in Figures 4 and 5 for the MoH and SOC analyses, respectively. The cost-effectiveness ratios of current treatment have been added to Figures 4 and 5 as possible thresholds. Using the cost-effectiveness ratio as a threshold is based on the assumption that if an ICER is less than the current average cost per MLY then it may be considered cost effective. From the MoH perspective the ICER is below the $31 144 threshold in 6% of scenarios. From the SOC perspective the ICER is below the $75 444 threshold in 87% of scenarios, suggesting that the incremental cost per willingness to pay may

Table 5 Summary of multivariate (Monte Carlo) sensitivity analyses*

Mean	*Median*	*SD*	*Minimum*	*Maximum*	*25th percentile*	*75th percentile*
CEA						
Ministry of Health perspective						
$56 720	$50 029	$28 197	$21 833	$591 021	$39 810	$65 028
Societal perspective						
$50 141	$43 566	$29 094	$5 215	$524 539	$31 808	$59 691
CUA						
Ministry of Health perspective						
$325 939	$285 778	$164 713	$101 424	$2 320 583	$219 693	$383 927
Societal perspective						
$291 460	$249 380	$183 459	$16 824	$3 669 572	$177 802	$355 008

SD, standard deviation.

be reasonable, from the SOC perspective, considering the currently acceptable cost per MLY gained.

Discussion

This economic evaluation of Avonex® has included the results reported by Jacobs following an SDE, the available burden of illness data, and the quality of life evidence necessary to develop the first Canadian economic model for treatment following an SDE. The purpose of the model was to determine not only the benefit of treating patients with Avonex®, but also to determine the long-term benefits of treating patients following an SDE through the progression to the various CDMS severity levels. Due to the uniqueness of this model, we are limited in our ability to compare our results with others and were required to rely on the validity of our model. As such, we know that the progression through CDMS was similar in our model as compared to the criteria reported by Weinshenker.[17] In addition, we were able to approximate the time spent in the monosymptomatic state by applying the Kaplan–Meier curves reported by Jacobs.[3] The estimation for the progression to CDMS in the current treatment group was relatively low, but this only biased against the Avonex® arm, thus providing a conservative approach.

The cost of CDMS was compared to Canadian figures reported by Grima.[10] However, Grima did not report results for the monosymptomatic state. We were unable to find any additional Canadian studies to compare our calculated costs for the monosymptomatic state, and were required to rely on clinical expert opinion to estimate the burden of an SDE. Grima reported costs of $10 598, $12 903, $28 077, $26 193, $51 750 and $51 698 for EDSS 1–6 levels respectively. However, Grima did not include patients treated with interferon beta-1a and did not examine patients with a CDMS severity level greater than EDSS 6. Factoring in the higher cost of therapy, our cost estimates were also similar to those reported by Grima.[10]

Parkin and colleagues reported an incremental cost per QALY gained in a 10-year model of £228 300.[15] In comparison, our 15-year model resulted in an incremental cost per QAMLY gained of (CAD) $227 586. Approximat-

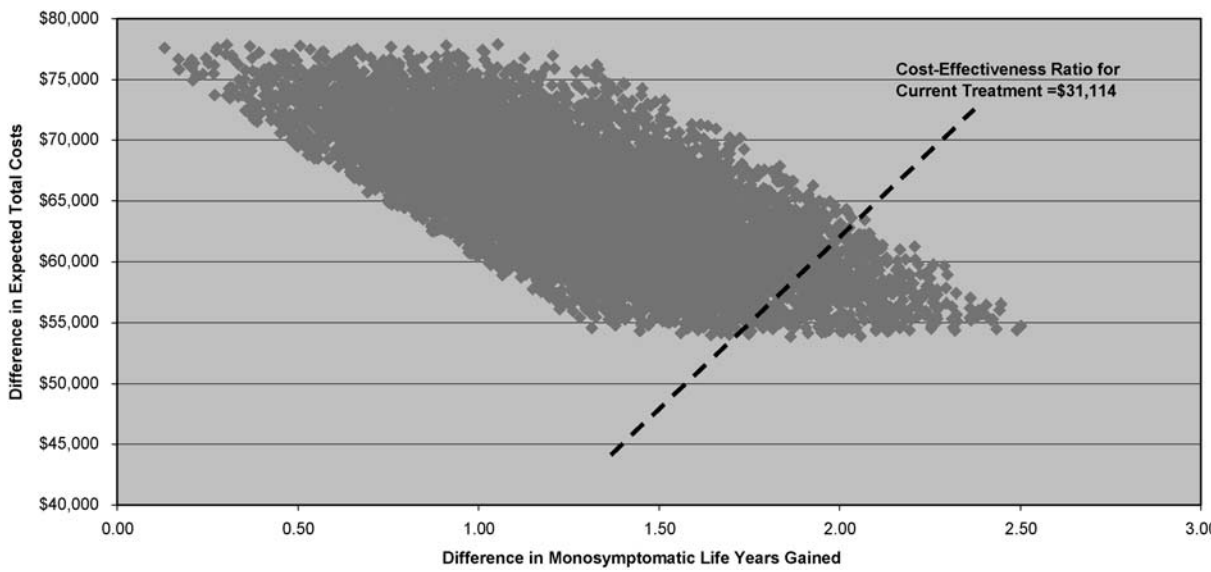


Figure 4 *Scatter plot of incremental cost-effectiveness ratios from the MoH perspective.*

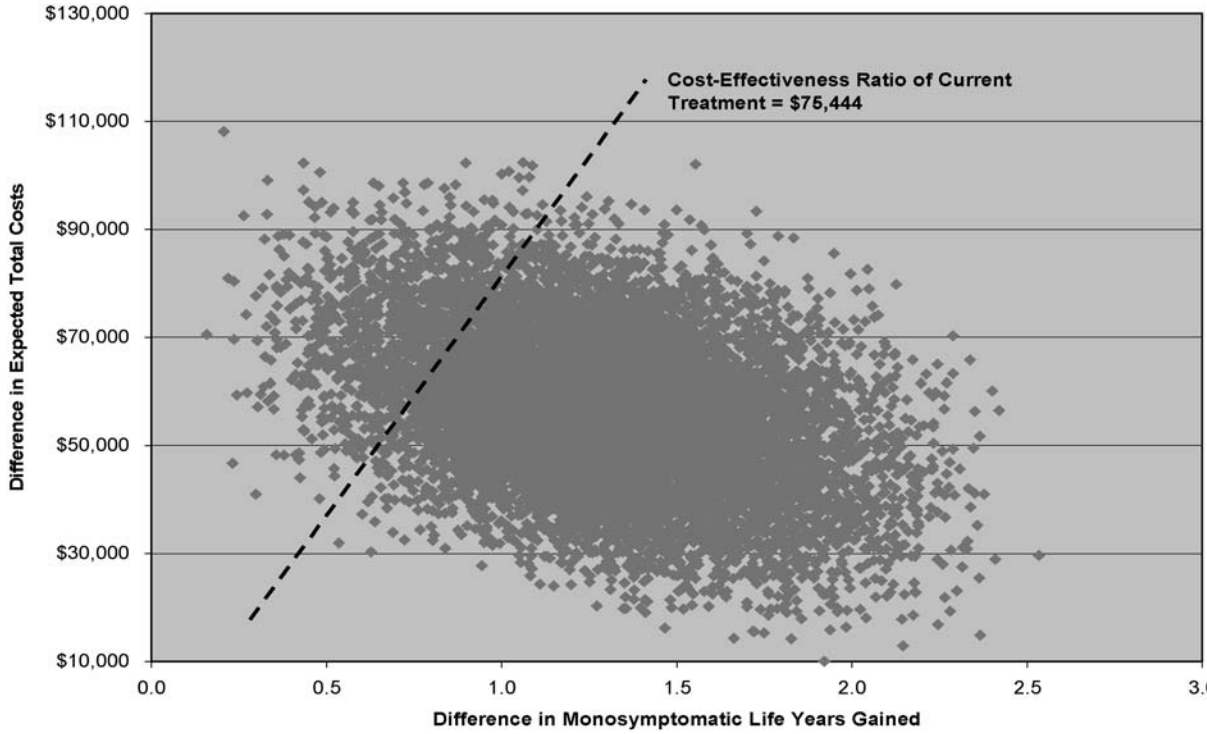


Figure 5 *Scatter plot of incremental cost-effectiveness ratios from the societal perspective.*

ing the Parkin figure into CAD would result in an incremental cost per QALY of $570 000, substantially higher than our figure. The cost-utility profile of interferon beta-1a was improved by the time spent in the monosymptomatic state, which was not modelled into the Parkin study. Thus, initiating treatment of Avonex® following an SDE should result in an improved long-term pharmacoeconomic profile of the treatment.

As would be expected, both models in the analyses were sensitive to the probability of progression into CDMS. In addition, the cost-effectiveness and cost-utility of Avonex®, compared to current treatment, improved as the time horizon was expanded, i.e., the longer the model the greater the improvement in the cost-effectiveness profile of Avonex®. This result was expected, as increasing the time horizon would allow for additional cost savings from the delayed progression to CDMS attributed to the Avonex® treatment arm; thus, longer analytic horizons may have been appropriate to capture all the benefits of the treatment. Both models were also sensitive to the indirect costs associated with the monosymptomatic state. This was expected because Avonex® delayed the progression into CDMS, thus delaying the progression into the higher burden states.

Results of the multivariate analyses from the societal perspective suggested that more than 87% of the scenarios would result in an incremental cost per MLY gained lower than the cost per MLY gained of current treatment. Therefore, the incremental cost for each additional MLY gained for Avonex® therapy would cost less than what is currently accepted. Results of the QAMLY multivariate analyses produced means that were higher than the base case result possibly due to skewness, as evidenced by the distributions of the multivariate analyses. More than 50% of the scenarios would result in an incremental cost per QAMLY gained lower than our base case result from both the MoH and SOC perspectives.

There are transferability issues with regard to generalizing the results of this study to other MS populations. However, the results could to some extent be extrapolatable to MS patients in other countries that have similar MS characteristics when compared with the MS patient population used in this study. In addition, those other countries would have to have similar reimbursement policies as those used in this study.

Conclusions

Treatment with Avonex® has been reported to delay the progression to CDMS following an SDE. The evidence provided by this pharmacoeconomic evaluation suggests that treating patients with Avonex® following an SDE could not only provide decreased morbidity and improved quality of life to the patient in the immediate time frame, but also suggest a relative cost-effectiveness for Avonex® over a 12-year period. In addition, the long-term benefits of treatment with Avonex® following an SDE, and continuing treatment through the various severity levels of CDMS improved the pharmacoeconomic profile of Avonex® compared to previous studies of Avonex® in CDMS alone.

Acknowledgements

Funding for this work was provided by Biogen Idec Canada Inc., Mississauga, Ontario, Canada. The clinical expert was Dr Trevor Gray and the pharmeconomic experts were Dr Thomas R Einarson and Michael Iskedjian. Colin Vicente is currently working at Bayer HealthCare Canada, Toronto, Ontario, Canada.

References

1 Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC *et al*. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983; **13**: 227–31.
2 McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD *et al*. Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001; **50**: 121–27.
3 Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownscheidle CM, Murray TJ *et al*. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. *N Engl J Med* 2000; **343**: 898–904.
4 Fazekas F, Barkhof F, Filippi M, Grossman RI, Li DKB, McDonald WI *et al*. The contribution of magnetic resonance imaging to the diagnosis of multiple sclerosis. *Neurology* 1999; **53**: 448–56.
5 Optic Neuritis Study Group. The 5-year risk of MS after optic neuritis: experience of the optic neuritis treatment trial. *Neurology* 1997; **49**: 1404–13.
6 Morrissey SP, Miller DH, Kendall BE, Kingsley DP, Kelly MA, Francis DA *et al*. The significance of brain magnetic resonance imaging abnormalities at presentation with clinically isolated syndromes suggestive of multiple sclerosis. A 5-year follow-up study. *Brain* 1993; **116**: 135–46.
7 O'Riordan JI, Thompson AJ, Kingsley DP, MacManus DG, Kendall BE, Rudge P *et al*. The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up. *Brain* 1998; **121**: 495–503.
8 Rudick RA, Goodkin DE eds. *Treatment of multiple sclerosis: trial design, results, and future perspectives*. New York: Springer Verlag, 1992: 49–51.
9 The Canadian Burden of Illness Study Group. Burden of illness of multiple sclerosis. Part I: cost of illness. *Can J Neurol Sci* 1998; **25**: 23–30.
10 Grima DT, Torrance GW, Francis G, Rice GP, Rosner AJ, Lafortune L. Cost and health related quality of life consequences of multiple sclerosis. *Mult Scler* 2000; **6**: 91–98.
11 Kobelt G, Jonsson L, Miltenburger C, Jonsson B. Cost-utility analysis of interferon beta-1B in secondary progressive multiple sclerosis using natural history disease date. *Int J Technol Assess Health Care* 2002; **18**: 127–38.
12 Nuijten MJC, Hutton J. Cost-effectiveness analysis of interferon beta in multiple sclerosis: a Markov process analysis. *Value Health* 2002; **5**: 44–54.
13 Henriksson F, Fredrikson S, Masterman T, Jönsson B. Costs, quality of life and disease severity in multiple sclerosis: a cross-sectional study in Sweden. *Eur J Neurol* 2001; **8**: 27–35.
14 The Canadian Burden of Illness Study Group. Burden of illness of multiple sclerosis. Part II: quality of life. *Can J Neurol Sci* 1998; **25**: 31–38.
15 Parkin D, Jacoby A, McNamee P, Miller P, Thomas S, Bates D. Treatment of multiple sclerosis with interferon B: and appraisal of cost-effectiveness and quality of life. *J Neurol Neurosurg Psychiatry* 2000; **68**: 144–49.
16 Canadian Coordinating Office for Health Technology Assessment. *Guidelines for economic evaluation of pharmaceuticals: Canada*, second edition. Ottawa, ON: Canadian Coordinating Office for Health Technology Assessment (CCOHTA), 1997.
17 Weinshenker BG, Bass B, Rice GP, Noseworthy J, Carriere W, Baskerville J *et al*. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. *Brain* 1989; **112**: 133–46.
18 EuroQol Group. EuroQol: a new facility for the measurement of health related quality of life. *Health Policy* 1990; **16**: 208.
19 Ministry of Health. Ontario Drug Benefit Formulary Comparative Drug Index. Toronto, ON: Queen's Printer for Ontario, 2001.
20 Ontario Ministry of Health. Schedule of Benefits; Physician Services under the Health Insurance Act. Toronto, ON: Institutional Services Branch, Ministry of Health, 1993.
21 Ontario Ministry of Health. Schedule of Benefits: Laboratory services under the Health Insurance Act. Toronto, ON: Institutional Services Branch, Ministry of Health, 1993.
22 Ontario Ministry of Health. Ontario Case Costing Initiative: Case Mix Groups for 2001. Retrieved 5 November 2002, from: http://www.occp.com/data_analysis/fy98_99_00/FY0001forplex01.xls.
23 Statistics Canada. Employment, earnings and hours. *The Daily*, April 27, 2001. Retrieved 1 August 2003, from: http://www.statcan.ca/Daily/English/010427/d010427a.htm.
24 Sculpher M. The role and estimation of productivity costs in economic evaluation. In Drummond MF, McGuire A eds. *Economic evaluation in health care: merging theory with practice*. Oxford: Oxford University Press, 2001: 94–112.
25 Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownscheidle CM, Murray TJ *et al*. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. Internal Study Report, Biogen, 2000: Tables 16.2.6.1 and 16.2.6.2.
26 Briggs AH. Handling uncertainty in economic evaluation and presenting the results. In Drummond MF, Alistair M eds. *Economic evaluation in health care*, Oxford: Oxford University Press, 2001: 172–214.