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Modeling the cost-effectiveness of a new treatment for MS (natalizumab) compared with current standard practice in Sweden

G Kobelt[1,2], J Berg[3], P Lindgren[3,4], B Jonsson[5], L Stawiarz[6] and J Hillert[6]

Objective To estimate the cost-effectiveness of a new treatment (natalizumab) for multiple sclerosis (MS) compared with current standard therapy with disease-modifying drugs (DMDs) in Sweden.
Methods A Markov model was constructed to illustrate disease progression based on functional disability (the Expanded Disability Status Scale (EDSS)). The effectiveness of natalizumab was based on a 2-year clinical trial in 942 patients (AFFIRM). The effectiveness of current DMDs was estimated from a matched sample of 512 patients in the Stockholm MS registry. Patients withdrawing from treatment were assumed to follow the disease course of 824 patients with relapsing–remitting disease at onset in the Ontario natural history cohort. Costs and utilities are based on a recent observational study in 1339 patients. All data sets were available at the patient level. Main results are presented from the societal perspective, over a 20-year time frame, in 2005 Euros (€1 = 9.25 SEK).
Results In the base case, treatment with natalizumab was less expensive and more effective than treatment with current DMDs. When only healthcare costs were considered, the cost per quality-adjusted life year gained with natalizumab was €38 145. Results are sensitive only to the time horizon of the analysis and assumptions about effectiveness of natalizumab beyond the trial.
Conclusions This cost-effectiveness analysis used registry data, cohort and observational studies to extrapolate the efficacy findings of natalizumab from the AFFIRM clinical trial to measure effectiveness in clinical practice. The analysis results suggest that for the population considered, natalizumab provides an additional health benefit at a similar cost to current DMDs from a societal perspective.
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Key words: cost effectiveness; modeling; MS registry; multiple sclerosis; Sweden

Introduction

The introduction of new therapies increases alternatives for treatment, but novel and more efficacious treatments often come at a higher cost. Thus, in an environment where resources are finite, choices have to be made based on treatments' efficacy and their cost-effectiveness. Consequently, the majority of national healthcare payers in Europe, among them Sweden, demand economic evaluations (cost-effectiveness studies) as part of the information upon which decisions for resource allocation and reimbursement of new treatments are made [1]. The Swedish reimbursement authorities (LFN) further require that new treatments be compared with current standard therapy. However, clinical trials for market authorization are often carried out against placebo, and comparisons must thus be carried out indirectly, using either previous clinical trials with established treatments or, if available, data from

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patient registries. In such cases, the economic analysis involves modeling to allow different data sets to be combined.

Modeling is also generally required in chronic disabling diseases, as the majority of the effects on both costs and health outcomes and related quality of life (QoL) will be seen over the long term [2]. In multiple sclerosis (MS), costs increase and QoL decreases with worsening disease [3]. Potential savings and improvements in QoL will thus come from delaying or preventing progression to severe disease states associated with high costs and low QoL after a number of years, and can thus not be directly observed before the introduction of a new treatment. Clinical trials are short compared with the disease course, as it is neither efficient nor ethical to continue registration trials (that are often placebo-controlled) beyond the proof of efficacy. Effectiveness must hence be extrapolated beyond the clinical trial using additional data and making a number of assumptions.

Over the past decade, a considerable number of modeling studies have been performed in MS to estimate the cost-effectiveness of the current disease-modifying drugs (DMDs) versus symptomatic treatment [4–12], recognizing the fact that in this particular setting modeling is both adequate and required.

Natalizumab (Tysabri®), the first recombinant humanized anti-α-4 integrin antagonist, in a new class of selective adhesion-molecule inhibitors, has been shown in a clinical trial (AFFIRM) to significantly reduce the relapse rate and the likeliness of progression in patients with relapsing–remitting MS (RRMS) compared with placebo [12]. No direct comparison with current DMDs, Avonex (interferon β-1a), Betaferon (interferon β-1b), Copaxone (glatiramer acetate) or Rebif (interferon β-1a), is available. However, these drugs must be considered as standard therapy in Sweden for RRMS: the proportion of MS patients treated with these drugs is estimated at 30–35%, with usage in early disease of up to 60–70% [13]. The cost-effectiveness of natalizumab should therefore be estimated compared with current DMDs in order to respond to the demand of the authorities (LFN).

We propose an economic analysis where treatment with natalizumab as observed in AFFIRM [14] is compared with treatment with DMDs for a comparable patient group followed in the Swedish MS registry in the Stockholm area. For the economic evaluation, patients from the trial and the registry are matched on both demographic and disease variables (age, gender, disease duration and disease severity). The analysis thus applies to the setting of the clinical trial where natalizumab would be used instead of one of the current DMDs in Sweden.

Materials and methods

Building on our previous work in MS [7–9], a Markov model was developed that combines clinical, epidemiological and observational data, and estimates costs and outcomes over a period of 20 years. Markov models are the technique of choice in diseases with ongoing risk such as disease progression. In these models, patients are distributed into clearly defined and mutually exclusive states that describe their health. Health changes (improvements or deteriorations) are represented as the risk of transition to a different health state within a given time frame (cycle). Costs and QoL are assigned to these health states and accumulated over time for each patient as an area under the curve.

In our model, Markov states are based on the Expanded Disability Status Scale (EDSS) [15]. As disease progression is not linear, states are defined as 1 EDSS point (except between EDSS 6 and 7, where half a point is used). This corresponds to the efficacy criteria defined in the AFFIRM trial and captures all changes as measured within the trial. States are further split into 'on treatment' and 'off treatment' to allow for therapy discontinuation at any time. Including a state for death, each arm of the model thus contains 19 states. The cycle length was set to 3 months, in order to capture the 3-month EDSS measurements and relapse assessments in the AFFIRM trial. During each cycle, patients can have a relapse, discontinue treatment, change EDSS or die. Ideally, and according to guidelines from LFN and other authorities, simulations should be run over the lifetime in chronic diseases. However, considering the limited duration of the clinical trial, we set the time horizon to 20 years, according to what had been used in earlier assessments by health technology assessment bodies such as NICE in the United Kingdom [16].

A simplified structure of the model is represented in Figure 1.

Data

Effectiveness data for natalizumab

The effectiveness of natalizumab on relapse rate and disease progression was based on patient level data from the double-blind 2-year AFFIRM trial [14]. The trial enrolled 942 patients, randomly assigned to receive natalizumab (627 patients) or placebo (315 patients) by intravenous infusion every 4 weeks for more than 2 years. The primary endpoints were the rate of clinical relapse at 1 year and the rate of sustained progression of disability at 2 years.

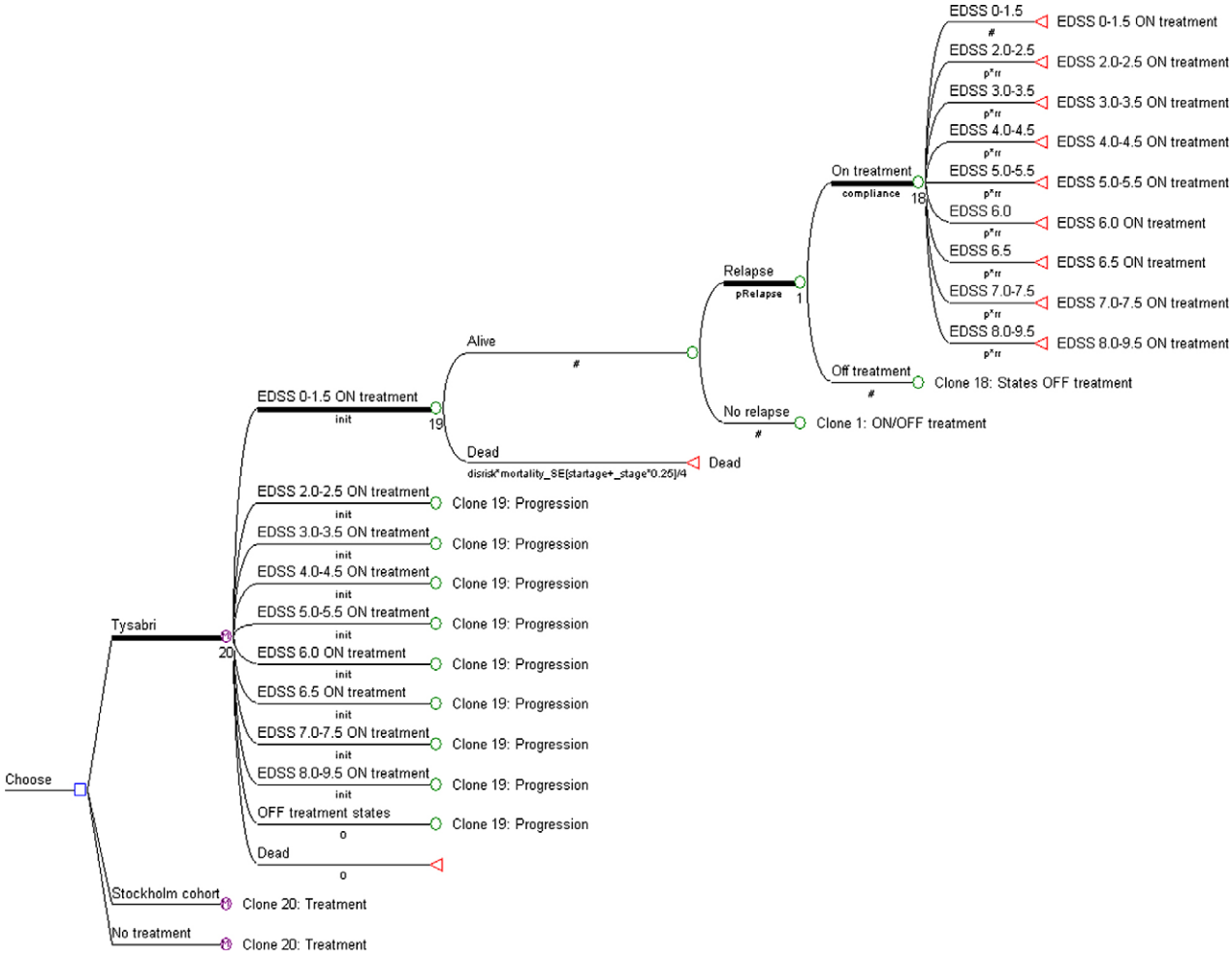

Figure 1 Outline of the model structure. At the start of the simulation, patients are distributed into EDSS states according to the cohort distribution in the clinical trial with natalizumab (see Table 2). During each cycle, the model verifies in all arms the probability of a patient experiencing a relapse, discontinuing treatment, dying according to MS specific mortality or changing their EDSS score. At the end of each cycle, patients are redistributed into the 19 states (9 on-treatment states, 9 off-treatment states, death) in each of the arms. The representation of the tree uses 'clones' for simplification: 'clone 20 Treatment' indicates each time that the arm contains the full structure shown for the Natalizumab arm; 'clone 19 Progression' indicates that the arm contains the full tree structure shown for the first state, EDSS 0–1.5; 'clone 1 On/Off Treatment' indicates that the arm contains the full structure shown at the node on–off treatment; 'clone 18 States off treatment' indicates that the arm contains the full structure with 9 states shown for patients on treatment.

Over 2 years, natalizumab significantly reduced the risk of sustained progression of disability by 42% (hazard ratio 0.58); the cumulative probability of progression was 17% in the natalizumab group and 29% in the placebo group. The rate of clinical relapses was reduced by 68% ($p < 0.001$) and led to an 83% reduction in accumulation of new or enlarged hyperintense lesions, as detected by magnetic resonance imaging (MRI). The annualized relapse rates were 0.23 in the natalizumab group compared with 0.73 in the placebo group.

The distribution into functional states at baseline and at the end of 2 years is shown in Table 1.

Effectiveness data for current DMD treatment

Individual data for patients treated in clinical practice in the Stockholm County were obtained from the Swedish MS registry (http://www.msreg.net). This national registry was officially established in 2001 and is funded in part by the National Board of Health and Welfare (http://www.socialstyrelsen.se). The registry is managed from the Karolinska University Hospital at Huddinge (Stockholm) where a local registry existed previously and was incorporated. Participation in the registry by clinical centers is voluntary, but it is estimated that

Table 1 Distribution into the Markov states of patients in AFFIRM and in the Stockholm MS Registry at start of treatment with DMDs and at last available follow-up

EDSS score	AFFIRM clinical trial ($n = 627$)		Stockholm MS Registry Sample ($n = 512$)	
	Distribution at baseline	Distribution at 2 years	Distribution at baseline	Distribution at last follow-up (mean 34 months)
0–1.5	33.5%	42.0%	49.5%	37.7%
2.0–2.5	33.2%	28.2%	27.4%	27.9%
3.0–3.5	20.7%	15.9%	18.5%	16.0%
4.0–4.5	9.6%	9.6%	4.6%	9.4%
5.0–5.5	2.9%	2.6%	0%	3.3%
6.0	0.2%	1.2%	0%	2.0%
6.5	0.0%	0.3%	0%	1.4%
7.0 and above	0.0%	0.3%	0%	2.3%

about 60% of all patients in Sweden are included. Mandatory inputs are limited, but include detailed data on DMD treatment (cross-checked against patient charts). EDSS is usually assessed at least once per year by neurologists.

At the time of data extraction (October 2005), a total of 6878 patients were registered. Of these, 2031 were or had been treated with DMDs. Patients in the Stockholm area represented 42% ($n = 2878$) of the registry. The county represents approximately one-fifth of the Swedish population, which would indicate that virtually all patients in the area are included in the registry. The majority (92%) were followed at the Karolinska University hospitals. From this group we extracted patients who were alive, had at least one clinical visit recorded and had received one of the DMDs at any time during the follow-up ($n = 1316$). This sample was then further narrowed to match the patients with RRMS in AFFIRM. The selection process is illustrated in Figure 2.

We excluded patients with primary progressive MS, clinically isolated syndrome, an uncertain diagnosis and a current diagnosis of RRMS but an EDSS higher than 4.5 at the start of DMD treatment. The registry currently only maintains the current diagnosis, but work is ongoing to enter information on changes in the disease course, similar to the natural history cohort in Ontario. To avoid excluding patients who had progressed despite of treatment, we included patients with a current course of secondary progressive MS (SPMS), but an EDSS of 3.5 or lower at the start of DMD treatment, as it is likely that they had RRMS at that time.

The first visit at which DMD treatment was started was set as baseline for all patients. EDSS

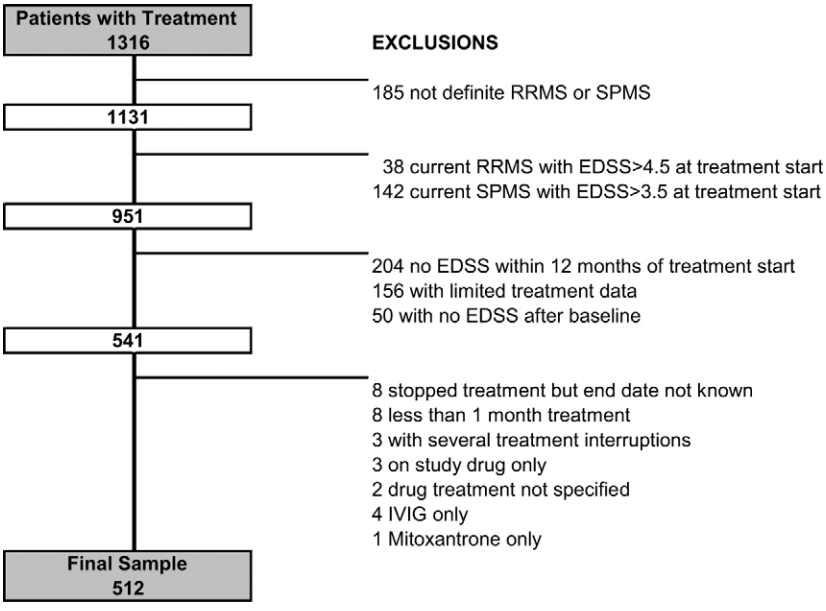

Figure 2 Selection of patients for modeling against natalizumab. For the modeling, patients that were similar to the patients in the natalizumab trials in terms of start of treatment were selected. From these, patients with incomplete EDSS or therapy data were excluded. The final sample included 512 patients of which 438 had RRMS and 74 SPMS at the last follow-up.

scores were available for 66% of these visits. For the remainder, we assigned the most recent score reported within a maximum of 1 year and excluded all other patients. Next we excluded all patients who had no second EDSS score after treatment start owing to either recent inclusion in the registry or recent treatment start. The remaining patients had one or two EDSS measurements per year and these scores were assigned to 3-month periods for the modeling; scores for quarters with no measurement were estimated with linear interpolation. The last visit on treatment with an EDSS measurement was set as the end of the follow-up, even if further visits were recorded.

Detailed therapy data were available, but switching was frequent, in part following the sequence of the introduction of the current DMDs. As the objective of our study was not a comparison with any given drug, but rather to the mixture of drugs as currently used, we defined patients 'on treatment' as those using any of the available drugs. Patients who had stopped treatment for more than 6 months, or who had switched to intravenous gammaglobulines (IVIG), mitoxantrone or an investigational drug, were included up to the end of the previous DMD. IVIG and mitoxantrone treatment was, however, included if used for a short time between two DMDs.

The final file contained 512 patients with a profile similar to patients in AFFIRM. The mean age at treatment start was 37.6 years. Time at onset of symptoms was 31.0 years (standard deviation (SD) 9.3, median 30), and 70.3% were women. The mean/median time of follow-up on treatment was 34.3/33 months, ranging from 3 to 132 months. The majority (438) had RRMS and 74 had SPMS at the last follow-up. The cohort distributions at baseline and at the end of the available (variable) follow-up time are shown in Table 1.

Natural history data

The Ontario data set including 824 patients with RRMS at onset had been used in a number of earlier disease models [8,9]. The mean follow-up time was 24.4 years, 69% were female and the average age at onset of MS was 28.6 years. The data set included annual EDSS scores and quarterly measures for the 3-month cycles in the model were derived using linear interpolation, as for the registry data.

Cost and utility data by EDSS level

Disease costs and utilities by EDSS level were calculated from the Swedish cohort of 1339 patients included in a recent international survey of MS sufferers in Europe [3, 13]. The study collected costs from a societal perspective, i.e. including medical and non-medical costs, patient costs, informal care and production losses. Medical costs included all MS-related inpatient and outpatient care, rehabilitation, tests and drugs. Non-medical costs included devices such as walking aids and wheelchairs as well as services provided by the healthcare system such as nurse visits, home help and personal assistants. Also included were costs borne by the patients (e.g. transformation to their home or car) or by their families (informal care). Production losses were based on short-term work absence and early retirement as a result of MS.

In the survey patients assessed their disease severity based on pre-tested descriptions of 10 disease states based on EDSS. A similar approach had been used earlier and been shown to yield accurate data when compared with patient charts [17]. Annual costs ranged from €16 000 at an EDSS below 2 to €116 000 at an EDSS of 8 or higher, and the cost of an average relapse was estimated at €3080.

Patients also completed the EQ-5D, a widely-used generic QoL instrument [18,19]. The questionnaire asks how patients fare in five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and answers are related to a health status description for which utilities have been established in the general population using standard methods [18]. Utilities represent a QoL index on a scale anchored between 0 (dead) and 1 (full health), and quality-adjusted life years (QALYs) are then calculated by multiplying years of life with their quality (utility). Utilities in the observational study ranged from 0.83 at an EDSS below 2 to 0.05 at an EDSS of 8 or higher. During a relapse, utility was decreased by an average 0.09.

Mean costs and utilities by state for the model were estimated for individual patients using multiple regression analysis with age, disease state and relapse as explanatory variables. However, for illustrative purposes, mean costs and utilities by state are presented in Table 2.

Model parameters

Transition probabilities

Transition probabilities from one Markov state to the other were calculated with ordered probit regressions to match the data sets. The probability of moving from state a to state b is defined as the probability of being in state b at time t, conditional upon being in state a at time $(t - 1)$ and controlling for age, gender, time since diagnosis, onset of

Table 2 Mean costs and utilities by Markov state (Sweden, $n = 1339$; 2005 Euro: €1 = 9.25 SEK)

EDSS score	Direct costs[a] (€)	Informal care costs (€)	Indirect costs[b] (€)	Utility (EQ-5D)
0–1	1813	406	4889	0.825
2	8457	1065	11 638	0.696
3	6142	1747	18 757	0.646
4	12 063	1627	12 774	0.61
5	15 458	3406	21 100	0.583
6	13 546	4297	20 422	0.572
6.5	21 515	6322	25 826	0.462
7	37 553	7113	27 247	0.373
8–9	77 574	12 061	33 144	0.047

[a]Excluding DMDs.
[b]Applied to patients below 65 years.

symptoms, relapses in the period before inclusion in the clinical trial and being on treatment or not.

Transitions for patients on treatment were estimated from the clinical trial and the registry for the duration of the observations. Probabilities were then extrapolated until the patients reach an EDSS score of 7 (at which time treatment ceased), with the assumption that the effect would be maintained for all drugs while on treatment. However, the clinical trial did not provide transitions beyond EDSS 6.5 owing to its short duration. We therefore used the transitions between EDSS 6.5 and 7 from the registry in both arms, thus imputing the effectiveness of standard DMDs to natalizumab at this level. The model accurately predicts the disease progression for patients on treatment with natalizumab or standard treatment for the periods for which data are available (Figure 3).

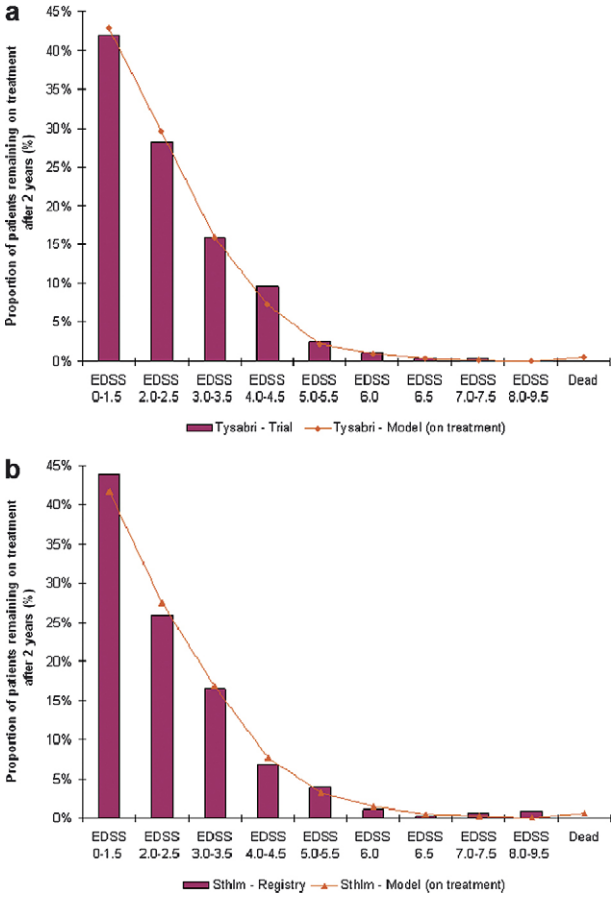

Figure 3 Model validation: (a) clinical trial; (b) MS registry. For the modeling, patients that were similar to the patients in the natalizumab trials in terms of start of treatment were selected. From these, patients with incomplete EDSS or therapy data were excluded. The final sample included 512 patients of which 438 had RRMS and 74 SPMS at the last follow-up.

Transitions for patients discontinuing treatment at any stage in both arms of the model, as well as EDSS changes above 7, were estimated from the natural history cohort in Ontario (Canada) [20]. The regression models are shown in Table 3.

Treatment discontinuation

Treatment discontinuation during the first 2 years was used as observed in both data sets for individual patients and was found to be similar in the trial and the registry (around 1.3% per quarter). After 2 years, discontinuation rates for both arms were estimated from the registry data using Weibull survival regression (Figure 4). Withdrawal rates increased over time, and the median time on DMD was estimated at around 6 years, ignoring switching between DMDs. (Of patients followed for more than 1 year, around half had used more than one DMD.)

Treatment cost

The quarterly cost for natalizumab was calculated as the drug cost and the cost for 13 infusions per year (€5700/quarter, €1 = 9.25 SEK). At the time of this analysis, it was not known what specific tests and monitoring would be required for natalizumab

Table 3 The regression models

Ordered probit regression results for clinical trial data						
state_next	Coef.	Robust Std. Err.	z	P>|z|	[95% Conf. Interval]	
_Istate_2	1.769823	.0622606	28.43	0.000	1.647794	1.891851
_Istate_3	3.167407	.0968909	32.69	0.000	2.977505	3.35731
_Istate_4	4.502389	.1304662	34.51	0.000	4.24668	4.758098
_Istate_5	5.402002	.2006173	26.93	0.000	5.008799	5.795205
_Istate_6	6.566355	.3275299	20.05	0.000	5.924408	7.208302
treated	-.0968134	.028387	-3.41	0.001	-.1524509	-.041176
age	.0117236	.0017565	6.67	0.000	.0082809	.0151663
yrspostDx	.0121329	.0024262	5.00	0.000	.0073777	.0168881
rlps_1yr	.030836	.0118874	2.59	0.009	.0075371	.054135
_cut1	1.462634	.0784259	(Ancillary parameters)			
_cut2	3.154803	.1006823				
_cut3	4.589106	.1244759				
_cut4	5.89006	.1661548				
_cut5	6.828793	.2141642				

Ordered probit regression results for Swedish registry data using all available observations						
state_next	Coef.	Robust Std. Err.	z	P>|z|	[95% Conf. Interval]	
_Istate_2	2.750379	.0869858	31.62	0.000	2.57989	2.920868
_Istate_3	5.456624	.1825426	29.89	0.000	5.098847	5.814401
_Istate_4	8.071683	.332439	24.28	0.000	7.420115	8.723251
_Istate_5	9.997236	.5419685	18.45	0.000	8.934997	11.05947
_Istate_6	11.48352	.592593	19.38	0.000	10.32206	12.64498
_Istate_7	13.21952	.9797483	13.49	0.000	11.29925	15.13979
age	.0045187	.0020487	2.21	0.027	.0005033	.0085341
yrspostDx	.0035179	.0028504	1.23	0.217	-.0020687	.0091046
_cut1	1.658192	.0824448	(Ancillary parameters)			
_cut2	4.383576	.1430015				
_cut3	7.024096	.253406				
_cut4	9.565139	.4148587				
_cut5	10.92821	.5231122				
_cut6	12.3268	.7451862				

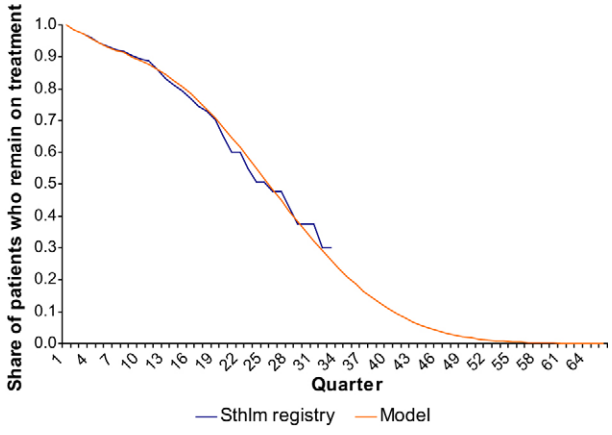

Figure 4 Treatment discontinuation in the registry. Follow-up in the registry ranged from 3 month to 11 years, but median follow-up was only 33 months. Treatment stop was known for 19% of patients and the remainder was on treatment at the last follow-up. Discontinuation rates were therefore estimated with Weibull survival analysis, resulting in a close fit with the observed rates.

owing to its rare but severe adverse event (progressive multifocal leukoencephalopathy (PML)) [19]. However, it was expected that patients would need to have a baseline MRI. We therefore (arbitrarily) assigned the cost of an MRI session (€388) to 50% of patients starting treatment, while the other 50% were assumed to have had recent MRI available. To test the potential impact of an intensive monitoring program, we chose to present a sensitivity analysis for a total cost increase of 20% (representing both additional monitoring and treating potential cases).

The cost of treatment with current DMDs was calculated as a weighted cost reflecting the total number of days of usage of each drug in the Stockholm MS registry. Patients included in the analysis used Avonex for 39.9% of therapy days, Betaferon for 11.4%, Copaxone for 10.7%, Rebif for 36.9% and IVIG or mitoxantrone for 1.1% of the days. This resulted in an average weighted quarterly drug cost of €3566, and no additional cost for administration was included.

Mortality

The model includes standard age and gender matched mortality rates for Sweden, as well as a relative disease-specific mortality risk due to MS (relative risk (RR) 3.0) [20,21].

Results

The main results are presented from the societal perspective, over a 20-year time frame, with both costs and effects discounted at 3%, in Euros (2005). Both arms start with the cohort distribution in the active group of the natalizumab trial.

Results for the base case and sensitivity analyses are presented in Table 4. Total costs in the two arms are similar, however, there was a small cost-saving of €3830 in the natalizumab arm. Patients in this group also have a better health outcome, represented by QALY gain of +0.34. Thus, with the same or slightly lower costs and a better effect, natalizumab dominates standard treatment.

Model robustness was tested using sensitivity analyses to explore the effect of following changes in a number of model parameters or assumptions: a healthcare cost perspective; increasing natalizumab costs by 20% to account for intensive monitoring for PML; increasing or decreasing natalizumab persistency (drop out rates between 2.5% and 7.5%) by 2.5%; decreasing natalizumab treatment effect; varying time horizons; and varying discount rates. As one would expect, the results suggest that the health effects in the model are sensitive only to the time horizon of the analysis and assumptions about treatment with natalizumab:

- Including only direct healthcare costs (excluding informal care and productivity losses): total costs are reduced in both arms but the potential for cost-savings are more limited. The extra cost for natalizumab is estimated at €13 000, leading to a cost per QALY gained of €38 000.

Table 4 Results and sensitivity analysis (2005 Euro: €1 = 9.25 SEK)

Scenario	Total cost (€)	Incremental cost (€)	Total effect (QALYs)	Incremental effect	Incremental cost per QALY gained (€)
Reference case					
Societal perspective, 20 years, 3% discount rate, persistence as in the trial or the registry					
Standard treatment	613 680		8.99		
Natalizumab	609 850	–3830	9.33	0.34	Dominant
Sensitivity analyses					
Only direct costs included (health care perspective)					
Standard treatment	339 165		8.99		
Natalizumab	352 175	13 010	9.33	0.34	38 145
Cost of natalizumab increased 20%					
Standard treatment	613 680		8.99		
Natalizumab	633 890	20 210	9.33	0.34	59 250
Higher and lower discontinuation rates					
Standard treatment (5%)[a]	623 423		8.91		
Natalizumab (2.5%)	647 839	24 416	9.34	0.43	56 811
Natalizumab (5.0%)[a]	618 647	–4776	9.24	0.34	Dominant
Natalizumab (7.5%)	608 263	–15 160	9.17	0.26	Dominant
Reduced treatment effect after the trial					
Standard treatment (as observed)	613 680		8.99		
Natalizumab (–5%)	621 455	7775	9.25	0.26	30 275
Natalizumab (–10%)	633 210	19 530	9.16	0.17	113 450
Different time horizons					
10 years					
Standard treatment	286 520		5.97		
Natalizumab	308 735	22 215	6.15	0.18	124 100
15 years					
Standard treatment	441 490		7.78		
Natalizumab	449 330	7840	8.05	0.27	28 835
No discounting					
Standard treatment	850 735		11.53		
Natalizumab	832 900	–17 835	11.99	0.46	Dominant
Discounted at 5%					
Standard treatment	502 180		7.73		
Natalizumab 7.5%/quarter	504 500	2320	8.01	0.28	8200

[a]Average rate rather than actual observed rate in the data sets, for comparison purposes.

- Increasing the cost of treatment with natalizumab by as much as 20% to account for potential extra costs due to intensive monitoring for PML [19]: the incremental cost is estimated at €20 000, with a resulting cost per QALY gained of €59 000.
- Varying treatment persistence with natalizumab after the trial: for this analysis, discontinuation rates were set at 5% in both arms (rather than actual variable rates as observed in the two data sets). The rate for natalizumab was then varied by 2.5% to understand the impact of treatment discontinuation. A discontinuation rate of 7.5% reduces the costs and although the health benefit is halved, natalizumab remains the dominant alternative. A rate of 2.5% increases costs, but also health benefits, resulting in a cost per QALY gained of €24 400.
- Reduced effect of treatment with natalizumab after the trial: in the absence of long-term effectiveness data for natalizumab (owing to termination of the trial following the PML detection), the base case assumes that effectiveness remains the same after 2 years. It is possible that effectiveness is increased or lost over time. A 10% reduction in effectiveness (both relapse reduction and progression) increases incremental costs to €19 500 and halves the QALY gain.
- Different time horizons: in the base case, the major difference between the arms is in outcome. As health benefits occur later rather than earlier, shorter simulations underestimate the potential benefit and thus reduce the cost-effectiveness of natalizumab.
- Different discount rates: higher discount rates reduce the value of the health benefit and the potential savings that occur late, while the effect on treatment costs that typically occur early is minimal. Cost-effectiveness ratios should thus increase. At the opposite end, no discounting increases the value of events that occur late and thereby the difference between the arms, and natalizumab remains dominant.

The interpretation of the results of the sensitivity analyses has to be done with care. As the difference in costs between the two arms in the base case is extremely small, even minimal changes in the parameters will affect the cost-effectiveness ratios rapidly. Results are sensitive, as expected, to discontinuation rates, assumptions about effectiveness after the trial and the duration chosen for the simulations.

Finally we explored the uncertainty in our estimates using acceptability curves (Figure 5). In the societal perspective, 55% of our estimates indicate that natalizumab is dominant and 75% remain below €50 000 per QALY gained. When only direct costs are included, almost 20% of the estimates remain cost-saving.

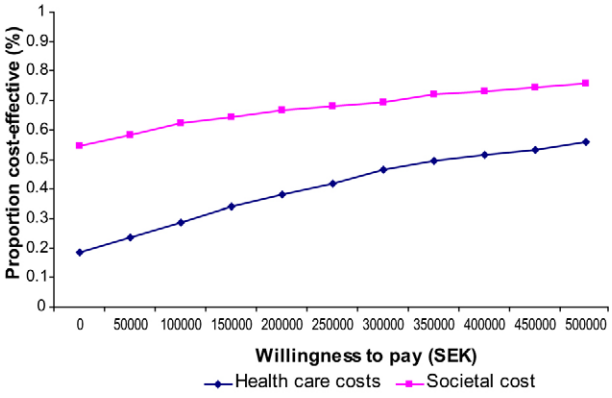

Figure 5 Illustration of uncertainty in the estimates. Acceptability curves are obtained with Monte Carlo simulation (10 000 runs) and illustrate the proportion of estimates that fall below given thresholds of willingness to pay for a QALY gained. In the societal perspective, 75% of all estimates fall below €50 000 per QALY (€1 = 9.25 SEK), while 55% of the estimates show cost-savings for natalizumab. When only healthcare costs are included, 55% of the estimates fall below the threshold of €50 000 and almost 20% show cost-savings.

Discussion

In this model we compared clinical trial results for natalizumab with treatment with a mixture of all currently available DMDs in clinical practice rather than with the placebo group from the same trial. A number of points in our analysis require discussion.

In Sweden a large proportion of patients with RRMS are currently treated with DMDs, and any new treatment should hence be compared with current standard treatment. Indeed the Swedish reimbursement authorities require such a comparison. The MS registry of the Stockholm area appears to include virtually all patients in the county and thus provides an excellent source of relevant data. In addition, data are collected by a small group of clinicians in one institution, which minimizes differences in data interpretation.

The type of comparison performed in this study, using patient-level data for all inputs, has to our knowledge not been performed previously for MS in Europe, and no benchmark exists. We minimized potential differences in the data sets. For instance, progression in the registry sample was defined as a change in EDSS confirmed at the subsequent measurement, regardless of the time lapse between the two measurements. As EDSS is measured on average once a year only in the registry, this may potentially underestimate the speed of progression. The

AFFIRM trial used the same criterion, but over a shorter time frame (3–6 months), thus potentially capturing progression earlier.

To further define a comparable patient sample to the AFFIRM trial patients, we excluded all patients who had started treatment at higher EDSS levels than those specified in the trial, those who had limited EDSS data after treatment start owing to recent enrollment and those who had been treated intermittently or with drugs other than DMDs. Also, patients with missing key variables (e.g. disease course) were excluded. Most of these patients came from the earlier follow-up at the Huddinge Hospital that had been incorporated in the registry. These patients were among the first to be treated with DMDs, and thus were likely patients with very active disease. Including these patients in our analysis could have biased the results in favor of natalizumab.

However, we included a number of patients with a current diagnosis of SPMS, despite the fact that the AFFIRM trial was performed in RRMS patients. The registry only maintains information on the current disease course, and complete data on conversions were not available at the time of data extraction. Limiting our sample to patients with current RRMS would have selected patients with stable disease and biased the analysis. We therefore assumed that patients with an EDSS level of 3.5 or less at treatment start had RRMS at that time. The assumption is based on an earlier analysis of conversion in the natural history cohort used in the model, where the majority of patients converted between EDSS scores of 3 and 6 (see [9]).

The final sample of 512 patients represents around 40% of patients treated at any time with DMDs in the Stockholm area. These patients represent a population that is similar to the patients in the clinical trial with natalizumab and may thus not be representative of the entire population in the registry. For the modeling, patients in the registry were matched with the trial patients for all available baseline demographic and disease variables (age, gender, disease duration, EDSS) to construct a population with the same baseline distribution as in the trial. Probabilities for progression were then estimated controlling for the same variables as well as the occurrence of a relapse.

One of the difficulties when using clinical practice data in MS is that the information relative to relapses may be incomplete, as patients do not always consult during an exacerbation. We therefore used the average relapse rate from the placebo group in the natalizumab trial as a benchmark, and applied the relative risk reduction from the active natalizumab arm (68%) and published clinical trials for the DMDs (about 30%) [21–24]. While relapses have a limited effect on cost-effectiveness ratios in the long term, as has previously been shown [8,9], they have an effect on progression early in the course of the disease [25–27]. Any such effect is thus integrated in the calculations of transition probabilities. As patients in the AFFIRM trial had more active disease compared with the published trial data of DMDs, and hence potentially a higher relapse rate, it is possible that the relapse reduction for the current DMDs is overstated.

As the open-label extension natalizumab trial was stopped owing to the appearance of two PML cases in MS, two key data inputs had to be based on assumptions: treatment persistency and longer-term clinical efficacy. For persistency, we assumed a similar treatment discontinuation pattern for natalizumab as observed from year 3 onwards in the registry. It is possible that this assumption may overestimate persistency, as it is to be expected that patients on natalizumab will be closely monitored and treatment will be stopped with any clinical suspicion of an opportunistic infection, thereby increasing the withdrawal rate. It should, however, be noted that sensitivity analysis indicates that a higher discontinuation rate would reduce costs and improve the cost-effectiveness ratios, and our assumption must thus be seen as conservative. For assumptions about the treatment effectiveness after the end of the trial period, we assumed that it would remain constant while on treatment, based on data on 3-year treatment (unpublished) that show a clear trend for a sustained treatment effect. Also, one would assume that patients where effectiveness diminishes are among those that withdraw from treatment. Thus, a reduced effectiveness might increase the withdrawal rate which would decrease the cost-effectiveness ratio: if patients remain on treatment but have, for example, a 10% faster progression, the cost per QALY would increase.

In the Swedish setting, and for patients such as those included in AFFIRM, treatment with natalizumab appears cost-effective under most assumptions. When testing uncertainty in the cost-effectiveness results, 75% of the estimates are below a threshold of €50 000 per QALY gained (corresponding to the value used by the Swedish traffic authority for a life [28]). As many as 55% of the estimates show cost-savings with natalizumab.

An important issue in this analysis is the inconsistency between the clinical trial and the approved indication. Natalizumab is to be used in patients who have not adequately responded to current DMDs, which is not the population of the AFFIRM trial. The regulatory approval thus implies that authorities accept that effectiveness would be similar. Two comparisons are relevant in this context: either to the second DMD or to no treatment. It was not possible to adapt our analysis to DMD failures, as effectiveness data for natalizumab in the

Table 5 Comparison of no treatment, current treatment and natalizumab (2005 Euro: €1 = 9.25 SEK). Base case: Societal perspective, 20 years, 3% discount rate, persistence as in the trial or the registry, patients not on treatment progress according to the natural history cohort (Ontario)

Scenario	Total cost (€)	Incremental cost (€)	Total effect (QALYs)	Incremental effect	Incremental cost per QALY gained (€)
No treatment[a]	623 570		8.39		
Standard treatment (compared with no treatment)	613 680	–9890	8.99	0.60	Dominant
Natalizumab (compared with standard treatment)	609 850	–3830	9.33	0.34	Dominant

[a]Based on placebo group of the AFFIRM trial for the first 2 years, extrapolated using patients from the Ontario natural history cohort.

second line are limited. Similarly, only about half of the registry sample had used two drugs or more and follow-up time on the second DMD was short. As an alternative, we have constructed a third identical arm in the model based on the placebo group in the AFFIRM trial (Table 5). Compared with no treatment, natalizumab remains dominant in the base case. Similarly, in a further indirect comparison of the placebo arm with current practice, DMDs are dominating no treatment. This analysis has to be regarded with caution, as the no-treatment arm is based on placebo patients from the AFFIRM trial followed by progression from the natural history cohort in Ontario. Nevertheless, this comparison would indicate that in a Swedish setting, standard therapy is cost-effective compared with no treatment and that natalizumab is cost-effective compared with standard therapy and no treatment. These results are based on modeling to help decision-making, and results can only be verified with time.

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