ORIGINAL RESEARCH ARTICLE

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Cost-Effectiveness Analyses of Natalizumab (Tysabri®) Compared with Other Disease-Modifying Therapies for People with Highly Active Relapsing-Remitting Multiple Sclerosis in the UK

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Supplementary Material

This supplementary material contains the appendices referred to in the full version of this article, which can be found at http://pharmacoeconomics.adisonline.com

Appendix A

The method chosen to model patients with highly active disease is based on the approach taken by Chilcott et al. (13) It models the natural history of the disease as a progression through a series of disability states, with relapse rates dependent on disability state. DMT is modelled as modifications to disability progression and relapse rates. Costs and utility per state are calculated from the number of patients within each state in order to derive the incremental cost-effectiveness ratio, and here we show how costs and utilities were calculated. Parameterization is provided in the main text.

Utility

The utility across the time frame of the model for the cohort, defined as U, may be broken down into three distinct parts. These are utility due to the natural history of the disease, $U_H(i,t)$, due to relapses in the cohort, $U_R(i,t)$, and due to adverse events, $U_A(i,t)$. The value for U can therefore be calculated across disability and disease states, i, at a given timestep, t, with a discount rate for benefits of d_u as

$$U = \sum_t \sum_i \left(U_H(i,t) + U_R(i,t) + U_A(i,t)\right).\left(1 + d_u\right)^{-t}$$

where i represents each of the EDSS scores for each of the RRMS disability states and for each SPMS disability state. $U_H(i,t)$ is dependent on the number of people in state i and the utility of a person in that state at time t. This may be broken down into $N_i(t)$, representing the number of people in state i that are receiving treatment, and $D_i(t)$, the number not receiving treatment at time t. The utility for a person in state i is based on a reference utility value u_i such that

$$U_H(i,t) = \left(N_i(t) + D_i(t)\right).\left(u_i + (Y_0 + t).u_d\right)$$

where Y_0 is the mean number of years since diagnosis at $t = 0$, and u_d is the change in utility per year since diagnosis. The expression for the change in utility due to relapses is given as

$$U_R(i,t) = (\beta.N_i(t) + D_i(t)).R_i.u_r$$

where β represents the relative rate of relapse, R_i is the average number of relapses per person in that state and u_r is disutility for a relapse.

$$U_A(i,t) = N_i(t).\left(\sum_s u_s.f_s(t) + g_i\right)$$

The expression for the utility for each state *i* for adverse events is given above and is simply the sum of the disutility per adverse event (u_s) multiplied by frequency of event ($f_s(t)$), where *s* is the number of adverse events that are included. Here we include disutility due to carers, as the term g_i.

Cost

The costs of the cohort across the timeframe of the model is denoted *C*. Cost is broken down by treatment, $C_T(i,t)$ and best supportive care costs of the disease $C_S(i,t)$. This is given below where d_c is the discount rate for costs

$$C = \sum_t \sum_i \left(C_T(i,t) + C_S(i,t)\right).(1+d_c)^{-t}$$

where

$$C_T(i,t) = (T_i(t) + \sum_s c_s.f_s(t)).N_i(t)$$

In this expression, $T_i(t)$ is the cost of treatment which includes all administration costs, and c_s is the cost of each adverse event due to treatment. State costs are based on the total costs due the disease and may be taken from a number of different perspectives. The expression for the state cost is given below and divided into costs associated with relapses for both patients on and off treatment, and the cost of being in state *i*,

$$C_S(i,t) = \left(\beta.N_i(t) + D_i(t)\right).R_i.c_R + \left(N_i(t) + D_i(t)\right).C_i(t) + \theta.N_i(t)$$

with $C_i(t)$ representing the basic supportive care cost in state *i* at time *t*, and c_R represents the cost of a relapse. For natalizumab, the cost of monitoring for PML and NAB are accounted for in the term θ.

Natural History

Progression of the cohort throughout the model is based on $N_i(t)$ and $D_i(t)$ which are both mid-year estimates, where

$$N_i(t) = \frac{n_i(t+1) + n_i(t)}{2}$$

and $n_i(t+1)$ represents the distribution of patients across EDSS scores at the end of year *t*, and is derived using the recursive relationship below

$$n_i(t+1) = \sum_j n_j(t).(1-\gamma).(1-\delta_j(t)).\alpha_{i,j}$$

For $n_i(0)$, the initial conditions are used. Individuals are removed due to withdrawals, γ, and deaths, $\delta_i(t)$. The constant $\alpha_{i,j}$ is the probability of transition each year from state j to state i.

$D_i(t)$ is calculated using the expression in a similar way to $N_i(t)$ using the expression below for $d_i(t+1)$. Here the withdrawals from the previous year are added to those that were previously withdrawn from treatment, mortality is then removed before undergoing transition. The mid-point estimates are then calculated using $d_i(t)$ and $d_i(t+1)$.

$$d_i(t+1) = \sum_j (d_j(t) + n_j(t).\gamma).(1-\delta_j(t)).\alpha_{i,j}$$

The parameter $\alpha_{i,j}$ represents the transition probability from state i to j and is composed of three parts. Transition probabilities for patients moving between SPMS states are unaffected by treatment. Patients that move from an RRMS state i to SPMS state $i+1$ in the absence of treatment with probability v_i, do so with probability $\frac{(1+\varepsilon_C).v_i}{2}$ where ε_C is the hazard ratio for disability progression on DMT. This formula is used as it models the assumption that there is a gradual progression of patients from RRMS to SPMS and that the hazard ratio is only applied to patients who are still RRMS. For patients moving between RRMS states

$$\alpha_{i,j} = \begin{cases} \alpha_{i,j} & i < j \\ 1 - \sum_{i \neq j} \varepsilon_C.\alpha_{i,j} - \frac{(1+\varepsilon_C).v_i}{2} & i = j \\ \varepsilon_C.\alpha_{i,j} & i > j \end{cases}$$

Appendix B

The PSA was undertaken by independently simulating costs, utility, efficacy, the rate of adverse events for treatments, initial EDSS distribution of patients and disability progression rates for the natural history.

Uncertainty surrounding cost parameters were sampled from a multinomial distribution; this was based on the covariance matrix generated from the seemingly unrelated regression fitted to the data. (3) Uncertainty surrounding health utilities were sampled from a multinomial distribution based the covariance matrix from the regression used to derive the utilities. (2)

Lognormal distributions were used to describe the uncertainty surrounding the relative estimates of efficacy and were based on the standard errors associated with these measurements in Table III. Sampled values of disability progression which were greater than 1 were capped at 1. Probability distributions used to describe the uncertainty in adverse event disutility due to treatment are based on the sample sizes (n = 19 for GA and n = 38 for IFN-beta (37)). The initial distribution of patients was varied using a Dirichlet distribution. Sample sizes for the distribution were taken as the sample sizes of the placebo arm of the ITT population in the AFFIRM study.

The transition probabilities of progression between RRMS states and between SPMS states were sampled using a Dirichlet distribution. Transition probabilities from RRMS to SPMS were sampled using a beta distribution.

Further details of the PSA are included in the manufacturer submission of the cost-effectiveness model to NICE (20). The model was iterated 10 000 times for each of the treatments.

Appendix C

A regression model was fitted to the data from the UK MS Survey (2, 3). The coefficients from the regression model are shown in Table C.1. and were used in the manufactures submission to NICE (20). All costs are for 2006.

Table C.1. Costs associated with different disease and patient characteristics for different cost perspectives (UK MS Survey 2005)

		Annual Cost		
Category	**Sub-category**	**NHS & PSS (£)**	**Governmental (£)**	**Societal (£)**
Score	EDSS 0.0	638	2682	16 541
	EDSS 1.0	927	3242	17 949
	EDSS 1.5-2.0	883	4288	23 176
	EDSS 2.5-3.0	2758	6849	28 958
	EDSS 3.5-4.0	1756	4753	22 657
	EDSS 4.5-5.0	2543	7452	30 598
	EDSS 5.5-6.0	3146	8604	32 166
	EDSS 6.5-7.0	7384	14 217	39 322
	EDSS 7.5-8.0	17 370	27 153	52 686
	EDSS 8.5-9.5	16 307	26 439	52 039
Type	RRMS	†	†	†
	SPMS	56	789	2916
Gender	Female	†	†	†
	Male	0	100	1577
DMT (IFN-beta)	No Treatment	†	†	†
	IFN-beta Treatment	8652	8652	8652
DMT (GA)	No Treatment	†	†	†
	GA Treatment	6202	6202	6202
DMT by EDSS State (IFN-beta)	With DMT in EDSS 0-2	†	†	†
	With DMT in EDSS 3-6	236	236	236
DMT by State EDSS (GA)	With DMT in EDSS 0-2	†	†	†
	With DMT in EDSS 3-6	-587	-587	-587
Age	Age	0	-49	-318

† Indicates that coefficient is reference value.

Utilities by EDSS state were also derived from data collected in the UK MS Survey 2005. The ED-5Q scores taken from patients were fitted using a multivariate regression, with EDSS score, disease type (either SPMS or PPMS) and year since diagnosis fitted covariates. The utilities derived are shown in Table C.2.

Table C.2. Utility for different EDSS states (UK MS Survey 2005)

EDSS State	RRMS	SPMS
0.0	0.91	0.87
1.0	0.84	0.80
1.5 to 2	0.74	0.70
2.5 to 3	0.61	0.57
3.5 to 4	0.65	0.61
4.5 to 5	0.56	0.51
5.5 to 6	0.49	0.45
6.5 to 7	0.44	0.39
7.5 to 8	-0.01	-0.05
8.5 to 9.5	-0.15	-0.19
Disutility associated with year since diagnosis		-0.0017 per year