The cost-utility of the rivastigmine transdermal patch in the management of patients with moderate Alzheimer's disease in the US

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Introduction

The management of Alzheimer's disease (AD) in the US is a major healthcare challenge, for which the costs are substantial. In the US there are more than 5 million people currently living with AD, and the total economic burden of AD is estimated to be around $100 billion annually, the majority of which is due to indirect costs of care and institutionalization[1]. Indirect costs of care include non-pharmacologic social support and assistance with activities of daily living (ADL), such as home caregiver assistance, support groups, community care, disease education and nursing home care. The cost of AD is expected to rise considerably as the aging population grows.

Currently, cholinesterase inhibitors, such as rivastigmine (Exelon®, Novartis), donepezil (Aricept®, Eisai) and galantamine (Razadyne®, Johnson & Johnson) and NMDA receptor antagonist memantine (Namenda®, Forest), form the mainstay of pharmacologic therapies to attenuate the symptomatic progression of AD patients.

In 2007, a novel, once-daily rivastigmine transdermal patch was approved in the US for the treatment of mild-to-moderate AD and Parkinson's disease dementia (PDD), and in the EU for the treatment of mild-to-moderate AD. The rivastigmine patch provides comparable exposure to the highest doses of capsules (12 mg/day) with improved tolerability, allowing easier access to optimal therapeutic doses. This in turn has the potential to improve treatment outcomes.

This analysis aimed to evaluate the cost-utility of the rivastigmine transdermal patch from the perspective of a US payer, and to provide evidence to support reimbursement of the rivastigmine patch in the treatment of AD.

Objective

The aim of this analysis was to model the incremental costs and benefits associated with the rivastigmine transdermal patch *versus* best supportive care (BSC) in the management of AD, from the perspective of a US healthcare payer.

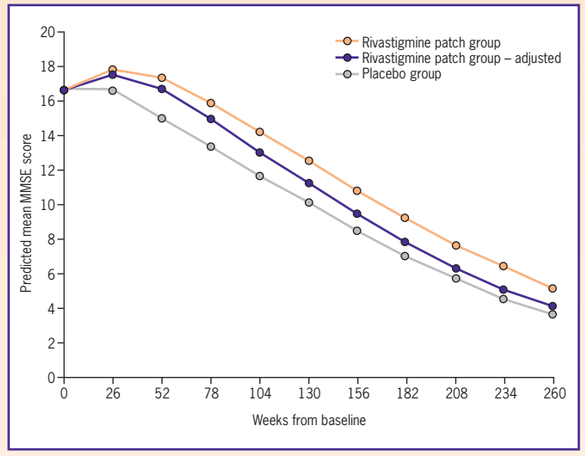
Methods

The cost-utility of the rivastigmine patch was assessed using an Excel-based economic evaluation model developed to compare incremental costs and Quality Adjusted Life Years (QALYs) associated with treatment.

The findings of the IDEAL study[2] (Investigation of transDermal Exelon in ALzheimer's disease), a 24-week randomized double-blind clinical trial with a 28-week open label extension, provided the efficacy data for the modeling analysis (focusing on 9.5 mg/24 h patch treatment groups). The clinical pathway for the current model was populated with data from the IDEAL study. Rivastigmine patch data came from patients who received patch for 12 months during the double-blind and open-label extension phases of the IDEAL trial (n = 383). Placebo data came from patients who received placebo during the double-blind trial (n = 282).

To model the patients' clinical pathway (Figure 1), two assumptions were made: (a) that a certain number of patients would discontinue treatment, and (b) that some patients would die. In the IDEAL trial, a discontinuation rate of 21.8% was reported for the 9.5 mg/24 h patch[2]. Similar rates were applied for the entire 5-year economic analysis, with adjustments to correct for any drop-out bias resulting from discontinuations of rivastigmine treatment.

Figure 2. Predicted MMSE scores using data from a 24-week, randomized clinical trial extrapolated for up to 5 years (9.5 mg/24 h rivastigmine patch treatment group; 9.5 mg/24 h rivastigmine patch treatment group adjusted for dropout bias; placebo group).



Mortality rates reported in the IDEAL trial were substantially lower than those published in epidemiological studies. The cost-utility model incorporated the mortality rates from epidemiological studies, and not those from the IDEAL trial, to reflect the application of the model to real-world clinical practice.

Disease progression was modeled using Mini-Mental State Examination (MMSE) scores extrapolated over a 5-year period by fitting Mendiondo curves[3] to the IDEAL data to obtain a suitable algorithm (Figure 2).

Utility gains were calculated using prior evidence correlating health-related quality of life (HRQoL) directly to MMSE score. Health Utilities Index Version 3 (HUI3)[4] point estimates were regressed to derive the following equation, which was then used for the base case:

$$\text{Utility} = -0.2392 + 0.0266 \bullet \text{MMSE}$$

QALYs were then calculated by applying this regression function to the mean MMSE score for each cycle of observation, and then multiplying by 0.5 to adjust for the 6-month cycle length.

The probability of nursing home placement (NHP) was estimated using the figures reported by Hauber *et al*[5], who built a piecewise Cox proportional hazard model to predict the likelihood that an individual will be institutionalized at a given MMSE for given values of covariates such as age, race and marital status. The Hauber *et al* model specifies the hazard rate (the likelihood that an individual will be institutionalized) at time t for a given covariate vector X as: $h(t) = h0(t)e^{\beta X}$, where h(t) is the hazard rate at time t when the covariate is X, h0(t) is the hazard rate at time t when the covariate is 0, X is the vector of covariates, and β is a vector of unknown parameters to be estimated.

Table 1. Input parameters for the base case cost-utility and sensitivity analyses in the US.

Parameter	Base case value	Sensitivity analysis
Probability of NHP[5,8]	Hauber model[a]	0.490 – 0.014 • MMSE
Mortality rate (per year)[9]	8.9%	Hazard ratio due to AD (HR = 1.4)
Discontinuation rate	21.8%	
Costs, $		
Drug[Novartis, 2007]	$2,492 pa	$2,990 (+20%)
Institutionalization[7]	$55,380 pa	$63,580 pa
Community care[7]	$12,309 pa	$13,318 pa
Informal care[6]	$0	$, Dependent upon MMSE
Time horizon	5 years	3 years
Utility[4,10]	–0.2392 + 0.0266 • MMSE	0.1395 + 0.0227 • MMSE
Stopping rule for treatment	No stopping rule	MMSE < 10
Discount rate for costs and benefits	3.5%	0%

NHP: Nursing Home Placement; pa: per annum.
[a]Cox proportional hazard model[5]

The number of institutional days avoided was derived from the probability of NHP, and was calculated as the difference between the average number of days/year a patient spent in an institutional setting for the rivastigmine and placebo arms.

Incremental costs in the model included: drug costs, costs of institutionalization and community care costs. Costs of informal care were not included in the base case cost-utility calculations, but were included in the sensitivity analysis. Costs of informal care were assumed to be higher in the community *versus* the institution[6].

Costs of institutionalization for the base case were derived from the average direct healthcare costs of all patients living in nursing homes or in assisted living facilities[7]. Community care costs for the base case were derived from the average direct healthcare costs of patients in managed care settings or in academic medical centres[7].

Input parameters for the base case cost-utility analysis are summarized in Table 1. Costs were converted to year 2006 values, and a discount rate of 3.5% in the base case was applied. Base case analysis did not assume any MMSE-based stopping rule for treatment. One-way, deterministic sensitivity analysis was used to look at the effect on the model when using different values for drug costs, utilization parameters, event rates and utilities, varying one parameter at a time. The following regression – based on the relationship between the Health Utilities Index Version 2 (HUI2)[4] and MMSE – was used:

$$\text{Utility} = 0.1395 + 0.0227 \bullet \text{MMSE}$$

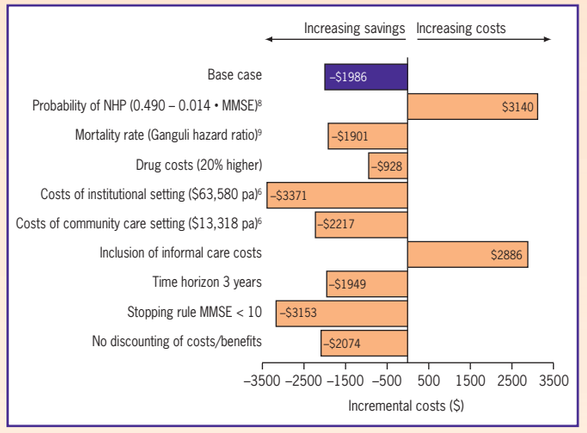
Results

The mean MMSE at baseline for patients modeled was similar for both the rivastigmine patch (16.7) and placebo (16.4) groups, and indicated moderate AD.

From the perspective of a US payer, the base case cost-utility model predicted that the rivastigmine transdermal patch (9.5 mg/24 h) would provide an incremental 0.09 QALYs, help avoid 64.3 institutional days over 5 years, and save $1,986 per patient (Table 2).

One-way sensitivity analysis suggested that the results were consistent with varying parameters. The main determinants of the cost-effectiveness ratio were: the likelihood of institutionalization; the relationship between MMSE states and quality of life; and the analytic perspective adopted. Rivastigmine patch proved to be a dominant strategy, resulting in cost savings, in the majority of sensitivity analyses (Figure 3).

Figure 3. Results for one-way deterministic sensitivity analyses on the base case cost-effectiveness of the rivastigmine patch from a US perspective.



Since patients on the rivastigmine patch arm stayed in the community longer, resulting in delayed institutionalization, inclusion of informal care costs raised the cost-effectiveness ratio to $30,899 per QALY gained. Inclusion of informal care, however, did not consider treatment-related benefits and potential cost-offsets from reduced caregiver burden, etc.

Table 2. Base case cost-utility of the 9.5 mg/24 h rivastigmine patch *versus* best supportive care for the treatment of AD in the US.

	9.5 mg/24 h rivastigmine patch	Best supportive care	Incremental change
Benefits			
QALYs gained	0.3063	0.2129	0.09
MMSE improvement	90.50	83.48	7.02
Mean survival, years	4.00	4.00	0
Costs, $			
Drug	5,289	0	5,289
Institutionalization	108,230	117,584	-9,354
Community care	22,123	20,044	2,079
Total	135,642	137,628	-1,986
Cost-utility of 9.5 mg/24 h rivastigmine patch *versus* best supportive care			
Incremental cost per QALY gained			–$21,264
Incremental cost per MMSE scores gained			–$283
Number of institutional days avoided over 5 years			64.3

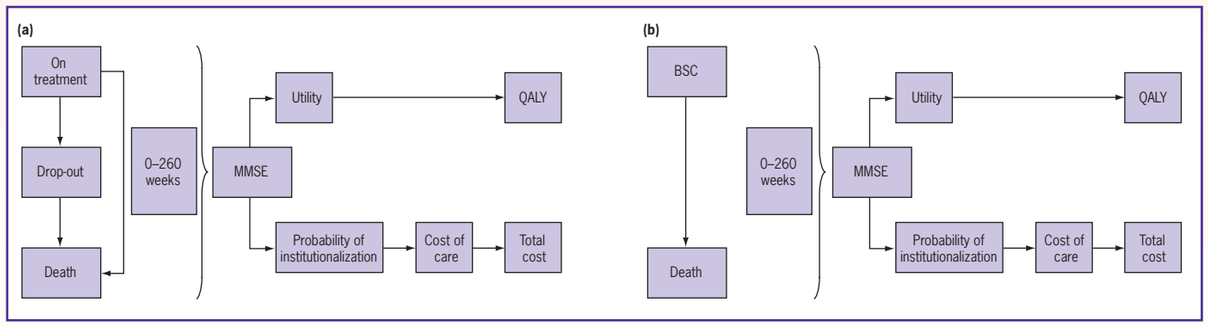
Discussion

Using this model, rivastigmine patch, from the perspective of a US payer, was calculated to achieve cost savings for AD patients. Rivastigmine patch is considered to be a cost-effective treatment for AD.

The main limitations of this analysis relate to the evidence available to quantify long-term efficacy and the costs and consequences of treatment. While an MMSE score is a standard measure of cognitive function, physical functioning scales (ADL) could offer another potential means for analysis where data are available. Secondly, estimates of the probability of institutionalization are variable within the literature, although sensitivity analyses provided consistent results favoring cost-effectiveness of rivastigmine patch.

In conclusion, using this model the rivastigmine patch demonstrated a favorable cost-effectiveness profile, well within the range of currently accepted thresholds for cost-effectiveness by US healthcare providers.

Figure 1. Clinical pathways for (a) patients receiving rivastigmine treatment, and (b) patients receiving best supportive care (BSC).



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