Modeling the Cost-Effectiveness of Galantamine for Mild to Moderately Severe Alzheimer’s Disease in Korea

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ABSTRACT

Objective: The aim of the study was to determine the cost-effectiveness, from the third-party payer viewpoint, of galantamine compared with usual care in the treatment of mild to moderately severe Alzheimer’s disease (AD).

Methods: An existing Markov model was adapted to Korea to predict long-term outcomes over a 5-year time horizon and to estimate the cost-effectiveness of galantamine for the treatment of AD. The model structure is informed by a review of national and international literature on the clinical and cost-effectiveness of galantamine and on the costs and outcomes associated with treatment for AD. The main outcome measure used was the cost per quality-adjusted life year (QALY) gained. All costs were indexed to US$ (2007 value). Multivariate probabilistic sensitivity analysis and scenario analysis were undertaken to assess uncertainty in the results.

Results: The study findings indicate that the clinical benefits on AD progression from galantamine treatment resulted in an incremental cost per QALY gained of US$4939 over 5 years (vs. usual care). Probabilistic sensitivity analysis and cost-effectiveness acceptability curve suggest that the probability of galantamine treatment having an incremental cost per QALY over US$6740 is zero. Incremental cost per QALY gained according to scenario analyses ranged from US$2271 to US$8335. Conclusion: These findings suggest that the use of galantamine may be a cost-effective use of Korean national health-care resources, considering the gross domestic product per capita of US$21,695 in 2007.

Keywords: Alzheimer, cost-effectiveness, galantamine, Korea.

Introduction

Alzheimer’s disease (AD) is the most common cause of dementia in Korea [1]. AD is placing substantial medical, social, psychological, and financial burdens on patients, their families, and their communities. The number of dementia patients in Korea is estimated over 400,000 in 2008, and projected over 1 million in 2030 [2]. As opposed to people with mild physical handicaps, people affected by even mild dementia need assistance and some surveillance. Moreover, people suffering from severe dementia require high-level, specialized care. AD progresses dramatically. In 3 years, 54% of people affected by AD reached the severe stage as according to the Clinical Dementia Rating Scale (CDR) [3]. Community-based care for patients with dementia is an explicit policy preference today. Community services are an essential part of living with dementia. They are necessary in order to impact positively on the quality of life of both people with dementia maintaining their independence and dignity, and the caregivers who need support with and respite from the duties of caring. Residential care services are also a necessary part of the continuum of services for people in the more advanced stages of dementia. Current economic pressures on available resources and especially concerns about the future resource pressures have attracted growing attention on the costs and cost-effectiveness of prescribed Alzheimer’s drugs and community and residential care.

In Korea, cognitive impairment is first recognized by family members. They usually bring this problem to the attention of a specialist such as geriatric psychiatrist, geriatrician, or neurologist. More than 95% of physicians in Korea are board-certified, so that very few general physicians are working. Therefore, primary contact of patients is a specialist, not a general practitioner. The Mini-Mental State Examination is widely used so that very few general physicians are working. Therefore, primary contact of patients is a specialist, not a general practitioner. The Mini-Mental State Examination is widely used for dementia screening. If the screening test is positive, referral is often made to further diagnostic workup including neuropsychological test battery, laboratory screening, and brain imaging. Usually, after the diagnosis is established, internal referrals are made to a social worker, rehabilitation specialist or to a clinical trial program as well as clinical treatment by a specialist. Day care services are provided by community-based dementia centers, while residential care services are by nursing homes. Long-term care insurance scheme has provided both community and residential care services. Moderate cases with behavioral and psychological symptoms of dementia are treated with the addition of atypical neuroleptics usually, and only in severe cases are patients referred for day care or nursing home care. In Korea, the announced criteria for reimbursement of the cholinesterase inhibitors (i.e., donepezil, galantamine, and rivastigmine) require specific conditions (i.e., Mini-Mental State Examination score 10–26 plus CDR 1–2 or Global Deterioration Scale 3–5).

Galantamine is a cholinesterase inhibitor with a dual mode of action [4]. Clinical trials have shown galantamine to be effective and safe up to at least 3 years of treatment, and the drug was well tolerated [5–8].

Currently, no studies have assessed the long-term cost-effectiveness of galantamine in Korea. This study aims to determine the cost-effectiveness of galantamine in the treatment of mild to moderately severe AD over a 5-year time horizon by estimating costs and outcomes associated with galantamine treatment for AD compared with those of usual care with no Alzheimer’s drugs under the health-care system in Korea.

Methods

A cost-utility analysis was performed to examine the potential benefits of galantamine to people with AD, and thus calculates the incremental cost per quality-adjusted life year (QALY) gained by the introduction of galantamine compared to usual care without any Alzheimer’s drugs. This economic evaluation was performed from the third-party payer viewpoint.
The terms “galantamine OR reminyl” AND “Alzheimer” were searched, which were limited by “clinical trial” in Medline, Embase, and the Cochrane Database of Systematic Reviews, and some scientific databases in Korea (i.e., KMBASE [http://kmbase.medric.or.kr], KoreaMed [http://www.koreamed.org], Medical Library Information System [http://medlis.riss4u.net], Research Information Center for Health [http://richis.org], Korean Studies Information Service System [http://kiss.kstudy.com], and National Assembly Library [http://www.nanet.go.kr]). Additionally the bibliographical data of all included publications were checked for further studies. All included papers presented original data of clinical trials on the use of cholinesterase inhibitors for the treatment of AD, covering clinical effectiveness, economic evaluations, modeling methods, health-related quality of life, and resource use. The clinical, epidemiological, and economic data from Korean literature were preferred to inform the cost-utility analysis presented in this article [9–13]. When no data were found in Korean national literature, data in other countries were considered and the most frequently quoted ones in previous publications were chosen.

**Costs**

Cost data were primarily adopted from a 1-year prospective trial assessing clinical and economic benefits of galantamine in Korea, using, as a primary endpoint, proportion of AD patients who needed full-time care (FTC) after 1 year. The study has been described in detail elsewhere [10]. In brief, they collected data on the resource use of all medical and other community service to estimate costs. Resource use was measured using the adapted version of the Client Service Receipt Inventory [16]. Primary caregivers were asked to provide details of costs and costs that patients had used during the previous 2 months by face-to-face interview. Resources used included hospital and primary care services (inpatient, outpatient, day hospital, emergency room, community mental health center, general practitioner, community practice nurse, and medication), social care services (social worker, day care center, meals on wheels, and home care), accommodation, out-of-pocket purchase for self-support (private hire of a paid caregiver or a paid home helper, health food and supplement, etc.), caregiver time, and missed work of caregiver. Indirect costs were calculated using a replacement cost approach. Caregiver time was assessed using the caregiver time section of the Resource Utilization in Dementia questionnaire [17]. In order to have valued the 2002 average household help wage in Korea, equivalent to US$5.22 per hour [18]. The total costs were calculated by adding each cost for resource used by each patient. Unit costs for 2002 were obtained from national sources in Korea [19–22]. They reported that average annual costs per dementia patient who was either in pre-FTC or in FTC were US$6388 and US$7623, respectively. Full drug cost of galantamine 24 mg per day was assumed, so that monthly drug cost was US$173.3 in 2007 value. A report from the National Health Insurance Corporation in fiscal year of 2005 included the monthly cost of outpatient of US$30.6 in 2004 value [23]. All the costs used in the model are in 2007 values after conversion using the ratio of consumer prices index (e.g., value at 2007/ value at 2002). For probabilistic sensitivity analyses, parameter distribution should be determined. Cost usually shows left-skewed distribution. Gamma distribution possibly provides similar left-skewed distribution.

**Effectiveness**

The effectiveness data were primarily adopted from results of intent-to-treat analysis of the 1-year longitudinal study demonstrating a significantly higher frequency of FTC in the usual care group (22.2% after 52 weeks) than in the galantamine treatment group (5.4% after 52 weeks) [10].

**Model Structure**

The serious challenge when modeling cost-effectiveness of Alzheimer’s drugs is predicting disease progression and thereafter modifying disease progression based on the clinical benefits from treatment. The methods available to model disease progression have all raised serious concerns. The prime concern is the use of cognitive function as a proxy parameter to model disease progression, which was greatly criticized [24,25]. Therefore, cognitive function has not been used to model disease progression in this article. The Assessment of Health Economics in Alzheimer’s Disease (AHEAD) model was adapted in Korea to assess the economic impact of galantamine treatment, based on the need for FTC. FTC was defined as the consistent requirement for a significant amount of time (>16 h/day) for care and supervision, regardless of the locus of care or who provided the care. Originally, the AHEAD model used predictive equations to estimate the time until a state for FTC or death [26]. The predictive equation for and death was not adopted in this study because we could find data on the FTC and mortality in published Korean literature [27–29]. Unpublished data on mortality were also provided by a Korean researcher who has conducted a longitudinal community cohort study. A common mortality rate (1.138%/month) for all patients was applied in this study. Although it is accepted that there may be differences in mortality by age and severity, the data do not allow us to differentiate by these groups at the moment.

Markov models are particularly useful when a decision problem involves clinical changes that are ongoing over time. At any stage of AD, the patient may become sufficiently disabled to require FTC for almost all days. Treatment may modify the AD progression by slowing the rate of developing disability. In this Markov model to project the costs and utilities of AD over a 3-year time horizon, three states were supposed: 1) state before FTC required (pre-FTC); 2) state for FTC; and 3) death. Figure 1 presents an outline of the modeling. Markov Monte Carlo simulation was used to predict time to FTC and to death. In a first-order simulation, 1000 trials were performed to get an acceptably low level of error with half-cycle correction for both initial and final costs and utilities.

The main assumptions made in the model are as follows: 1) galantamine would have no impact on survival; 2) for the model

![Figure 1](image_url)
Cost-Effectiveness of Galantamine in Korea

Table 1  Model inputs for the cost-effectiveness analysis for galantamine compared with usual care in mild to moderately severe Alzheimer’s disease

<table>
<thead>
<tr>
<th>Model input</th>
<th>Value</th>
<th>Distribution</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galantamine (US$/month)</td>
<td>173.3</td>
<td></td>
<td>[20]</td>
</tr>
<tr>
<td>Cost per outpatient visit (US$) (SD)*</td>
<td>30.6 (15.3)</td>
<td>Gamma</td>
<td>[11,19,20,23]</td>
</tr>
<tr>
<td>Pre-FTC, cost per month (US$) (SD)*</td>
<td>532.3 (266.2)</td>
<td>Gamma</td>
<td>[11,18,19,21]</td>
</tr>
<tr>
<td>FTC, cost per month (US$) (SD)*</td>
<td>635.3 (317.7)</td>
<td>Gamma</td>
<td>[11,18,19,21]</td>
</tr>
<tr>
<td>Effectiveness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion in FTC after 1-year drug treatment</td>
<td>0.054 (0.027)</td>
<td>Gamma</td>
<td>[10]</td>
</tr>
<tr>
<td>Proportion in FTC after 1-year usual care</td>
<td>0.222 (0.111)</td>
<td>Gamma</td>
<td>[10]</td>
</tr>
</tbody>
</table>

*Assumptions made on the standard deviation in the absence of other information.
FTC, full-time care; SD, standard deviation.

over a 5-year horizon, galantamine treatment would not result in additional health resource use except drug cost (galantamine); 3) the proportions of AD patients in FTC following galantamine treatment and usual care were used to modify disease progression over time; 4) patients continued to receive galantamine while they are in the pre–full-time care (pre-FTC) health state and stop galantamine when they progress to FTC health state; and 5) galantamine had the effect to delay progression to FTC health state for 1 year, while after 1 year, slope of decline in galantamine group was the same as that in usual care group, regardless of galantamine treatment. Evidence for these assumptions is provided later in the Discussion section.

Health Outcome
The main health outcome measure was the QALY [30]. This was used as a measure of overall health-related quality of life, and was consistent with the preferred evaluation approach for cost-utility analysis. Benefits on health-related quality of life have not been shown in Korean literature. Health utilities for the model states (pre-FTC and FTC) were derived from published Neumann et al.’s data on AD [31]. The utility of pre-FTC (0.60) was derived from the results for patients with mild to moderate AD, whereas utilities for severe, profound, or terminal AD were used to calculate the utilities of FTC (0.34).

Discounting
In keeping with the previous publication on the same topic reflecting the recommendation from the National Institute for Health and Clinical Excellence (NICE) of the United Kingdom, discount rate were 6% for future costs and 1.5% per year for future quality of life.

Uncertainty Analyses
The multivariate probabilistic analysis is conducted to capture uncertainty in a range of random variables (Table 1). The probabilistic sensitivity analysis is based on a specified cohort of 1000 AD patients and 1000 trials using the second-order Monte Carlo simulation in the model. Uncertainty analyses also comprised scenario analysis against a range of other assumptions made in the model. The considered scenarios are as follows: 1) galantamine has the effect to delay progression to FTC health state for a different limited time (e.g., 6 months, 2 years, 3 years, and 4 years); 2) patients continue to receive galantamine treatment to death; 3) health utility at FTC health state is 0.40, higher value than Neumann et al.’s 0.34; 4) patients show different mortality rates (e.g., 0%, 50%, or 150% of the mortality used in the model); 5) different discount rates are applied (e.g., 0%, 3%, or 5%); and 6) when effectiveness derived from the per-protocol population are applied (e.g., control group 11.9%, galantamine group 2.7%).

Results
The primary outcome was cost per QALY gained as an Incremental Cost-Effectiveness Ratio (ICER). Incremental cost was US$5630 while incremental utility is 1.14 (Table 2). Therefore, at base case scenario, the ICER is US$4939/QALY (Table 3). The mean reduction in the time spent in the FTC health state (increased time in pre-FTC) is 4.6 months over 60 months. Further, after 60 months, 18.8% of the patient with usual care alone remained in the pre-FTC health state, as compared to 22.7% of the galantamine treatment group (difference = 3.9%). More than half of AD patients (56.4%) were alive after 60 months.

Uncertainty Analyses
The results of cost-effective analyses were presented in the form of incremental cost-effectiveness scatter plot and cost-effectiveness acceptability curves. By linking the probability that the intervention was cost effective at different levels of the willingness of the third-party payer for an additional outcome (QALY), cost-effectiveness acceptability curves substitute for confidence intervals. According to this acceptability curve, given a maximum acceptable ratio of US$6740 per 1 additional QALY increase, the probability that galantamine treatment is cost-effective compared with usual care is 1 (perfect) (Fig. 2). The scatter plot in Figure 3 shows the results of 1000 simulations with the incremental effectiveness plotted on the horizontal axis

Table 2  Cost effectiveness of galantamine compared with usual care in mild to moderately severe Alzheimer’s disease

<table>
<thead>
<tr>
<th></th>
<th>Galantamine plus usual care</th>
<th>Usual care alone</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time spent in FTC over 60 months</td>
<td>11.1 months</td>
<td>15.7 months</td>
<td>4.6 months</td>
</tr>
<tr>
<td>% of patients in pre-FTC at 60 months</td>
<td>22.7%</td>
<td>18.8%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Cost (US$)*</td>
<td>30,567</td>
<td>24,937</td>
<td>5,630</td>
</tr>
<tr>
<td>Utility</td>
<td>22.91</td>
<td>21.77</td>
<td>1.14</td>
</tr>
</tbody>
</table>

*2007 values expressed as US dollars.
FTC, full-time care.
Table 3  Effects of the sensitivity analysis on the cost effectiveness of galantamine compared with usual care in mild to moderately severe Alzheimer’s disease

<table>
<thead>
<tr>
<th>Results of sensitivity analysis</th>
<th>Cost per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case scenario</td>
<td>4939</td>
</tr>
<tr>
<td>Per-protocol population</td>
<td>4339</td>
</tr>
<tr>
<td>Duration of progression-delaying shift effect of galantamine 6 months</td>
<td>8335</td>
</tr>
<tr>
<td>2 years</td>
<td>3127</td>
</tr>
<tr>
<td>3 years</td>
<td>2515</td>
</tr>
<tr>
<td>4 years</td>
<td>2271</td>
</tr>
<tr>
<td>When patients continue to receive galantamine to death</td>
<td>6725</td>
</tr>
<tr>
<td>Assumptions on health state utilities, pre-FTC 0.60, FTC 0.40</td>
<td>6469</td>
</tr>
<tr>
<td>Mortality rate (% per year for all patients)</td>
<td>3417</td>
</tr>
<tr>
<td>0</td>
<td>4139</td>
</tr>
<tr>
<td>–50% of base case</td>
<td>5638</td>
</tr>
<tr>
<td>+50% of base case</td>
<td>5320</td>
</tr>
<tr>
<td>3% for both costs and utility</td>
<td>5367</td>
</tr>
<tr>
<td>5% for both costs and utility</td>
<td>5438</td>
</tr>
</tbody>
</table>

QALY: quality-adjusted life year; FTC, full-time care.

and the incremental cost on the vertical axis. The ellipse contains 95% of the simulations. The ellipse exclusively lies in the northeast quadrant, suggesting decision-makers should balance gain against the cost. Further uncertainty analysis against model assumptions and scenarios shows results that ICER values range from US$2271 to US$8335 per QALY.

Discussion

This study reports the ICER value of galantamine in the treatment of AD in Korea is an estimated US$4939 per QALY, which should be judged “accepted.” Generally speaking, there is a linear relationship between the Gross Domestic Product (GDP) of a country and willingness to pay for an additional QALY. In 2007, GDP per capita was US$21,695 in Korea. This study indicates that the use of galantamine for the treatment of mild to moderately severe AD may be cost-effective in Korea.

The cost-effectiveness of Alzheimer’s drugs is an important topic. In the United Kingdom, revised NICE guidance suggested that cholinesterase inhibitors were not cost-effective. Thereafter, people in the early or severe stage of AD are currently denied the only approved Alzheimer’s drug treatment because NICE ruled cholinesterase inhibitors are too expensive when considering their effectiveness [32]. Green et al. reported the cost per QALY of galantamine in the United Kingdom was £63,103 [33], which is more than 20 times in monetary value when comparing the ICER values for galantamine in Korea even though these values are not directly compared. It may be partly caused by differences in medical, community, and residential care services provided between Korean and the United Kingdom, different ways to define FTC, different data for modeling, different cultural viewpoints of value for money, and fluctuation in currency exchange rate. However, the same modeling methodology and assumptions at base case scenario were applied for the cost-effectiveness analysis.

The adapted AHEAD model for this study is different from the original model [26,34,35]. In the previous studies of Caro et al., the transition to FTC was modeled as a function of time and several patient characteristics (i.e., psychotic symptoms, extrapyramidal sign, score of cognitive scales, duration of AD, and onset before age 65) under the assumption that FTC is conceptually identical to the need for health-related facility care equivalent to that provided in a nursing home setting for those who were in more severe stage of AD [16,34,35]. However, in this study, FTC is simply defined as a state of need for care, expressed as caregiver time more than 16 h per day.

This operational definition of FTC has several important implications. First, FTC can be easily defined as a single event as it literally means in terms of time used, not in terms of severity of AD or locus of care. It may make us avoid possible biases caused by including some correlates related to FTC in the process of developing the predictive equation to simulate FTC [16,34,35]. Strictly speaking, caregiver time may not be able to be reduced as a function of several countable factors. For example, in addition to the patient’s own factors (i.e., level of cognition, dysfunction, and behavioral problem), too many other caregiver factors will influence on the caregiver time: 1) caregiver physical and mental health; 2) sociodemographic characteristics of caregivers (i.e., age, gender, level of education, duration of care till now, social class, and income); 3) preferred health resources (i.e., home visiting service, day care, and respite care); 4) tolerability to given care burden; 5) general attitude toward care (i.e., optimistic or pessimistic; feel rewarded or not rewarded); and finally 6) affec-

Figure 2  Cost-effectiveness acceptability curve for galantamine compared with usual care. Costs are in 2007 values. INB, incremental net benefit; WTP, willingness to pay; QALY, quality-adjusted life-year.

Figure 3  Incremental cost-effectiveness scatter plot, showing highly concentrated dots within 95% confidence ellipse when galantamine treatment is compared with usual care. QALY, quality-adjusted life year.
tion to the patient affected by AD. Too many factors can influence on the caregiver time as well as related costs. Caregiver time itself can be a robust single indicator of caregiver burden. Second, in general, the time of 16 h a day might be maximum for caring for patients because caregivers should spend time for their own essential activities of daily living (i.e., sleep, eating, grooming, toileting, and washing). Third, most caregivers were averse to institutionalization and continue to provide in-home care long after it is in their own best interests to cease [29,36]. Escalating care demands eventually prompt caregivers to place patients in residential care. It should not be considered that family care is a cost-free alternative to residential care. Instead, caregivers incur huge care burdens, including economic hardship, curtailment of social activities, emotional strain, and psychological distress [28,29,36]. Heavy caregiver burden will quickly convert into tangible costs for patients and caregivers such as institutionalization or hospitalization.

Mostly, primary endpoint of health economic studies is death. However, death is undesired as an endpoint for AD when cost-effectiveness analysis is performed, because use of Alzheimer’s drugs is not supposed to extend life expectancy of people affected by AD. Some researchers have reported no or weak association between the long-term use of ChEIs and survival [37–39], while a few other researchers have observed that the long-term use of cholinesterase inhibitors (ChEIs) might lead to lower mortality rates [40,41]. At this moment, it is rational to assume that ChEIs do not have more than symptomatic effects, use of which will not extend life expectancy. Therefore, more relevant surrogate endpoint should be found. Institutionalization has been most preferred surrogate endpoint because Alzheimer’s drugs are believed to delay progression and institutionalization [5–8,42]. However, institutionalization would be decided not only by disease progression, but also by other factors such as caregiver burden and social situation (i.e., marital status, presence of caregiver, and finance). Many people with severe dementia are being cared for at home rather than in a nursing home. This is especially true in developing countries. In Korea, 7 out of 10 persons with dementia who need residential care were cared for at home in 2003 [43]. Operationally defined caregiver time more than 16 h per day as an indicator for the FTC may be a good candidate for surrogate endpoint in the cost-effectiveness analysis of Alzheimer’s drugs.

The study has a number of further limitations. Financial and personal heavy burden of caregivers is obvious, which can be easily converted to tangible costs on the health-care system. However, the impact of galantamine treatment on caregivers was not considered. Expected costs of health-care use by caregivers’ diseases occurred during caring for AD patients were not included in this model. On the other hand, even though the best data were sought, the evidence base on the costs, effectiveness, and health outcomes related to AD is limited. There is uncertainty over parameter values used in the model, but these limitations are common to the cost-effectiveness literature.

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Guk-Hee Suh has no conflicts to declare.

References

3 Galasko D, Edland SD, Morris JC, et al. The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD). Part XI.