Economic and Clinical Benefits of Galantamine in the Treatment of Mild to Moderate Alzheimer's Disease in a Korean Population: A 52-Week Prospective Study

To evaluate the impact of galantamine treatment on the function, caregiver time, and resource used in the treatment of patients with mild to moderate Alzheimer's disease (AD), costs and outcomes were evaluated during a 52-week prospective, randomized, double-blind, community-controlled trial of galantamine. Patients received either galantamine treatment (n=72) or no treatment (n=66). The analysis was performed from a societal perspective. Galantamine treatment reduced time spent caring for the patients and maintained improved functional capacity, whereas, when no treatments were given, a great increase in caregiver time and progressive functional deteriorations were observed. Saved caregiver time was equivalent to 113 working days per year. After 52 weeks, mean total annual costs per patient were 14,735,000 Korea Won (KRW) (USD 12,315) for patients with galantamine treatment and 25,325,000 KRW (USD 21,166) for patients without treatment. Adjusted annual cost saving of galantamine treatment was 6,428,000 KRW (USD 5,372) when compared to no treatment (p=0.0089). Galantamine had a beneficial effect not only to slow functional decline in patients with mild to moderate AD, but also to save a substantial amount of costs, closely related to reduction in caregiver burden and decrease in caregiver time.

Key Words : *RCT; Randomized Controlled Trial; Double Blind Method; Trial; Galantamine; Caregivers; Alzheimer Disease; Function; Benefit; Economy*

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INTRODUCTION

Alzheimer's disease (AD) affects about 4-7% of people over the age of 65 yr in Korea (1). As patients with AD progressively lose autonomy with a functional decline, caregivers experience a progressively increasing care burden with concurrent social isolation.

Galantamine is a tertiary alkaloid with a proposed dual mode of action: competitive inhibition of acetylcholinesterase (AChE) and allosteric modulation of nicotinic receptors (2). The long-term efficacy of galantamine in delaying the decline in cognitive function, activities of daily living, and behavioral disturbances has recently began to be reported (3, 4).

However, few studies have focused on the long-term economic and clinical benefits of galantamine. This 52-week prospective study aims to investigate the economic and clinical effects of galantamine, especially focusing on the functional capacity, caregiver time, and resources used in patients with mild to moderate AD in a Korean population.

MATERIALS AND METHODS

Study design

The rationale, methods, and results of the 16-week double-blind, community-controlled trial have been described elsewhere (5). As with the original 16-week study, the extended 52-week prospective health economic study was also quasi-experimentally designed with a galantamine group (multi-center, randomized, double-blind, parallel-group from 3 study centers in Korea) and a community AD cohort as a control group. This prospective study evaluated the impact of galantamine treatment on costs and outcomes of caring for patients with mild to moderate AD who lived at home. The same methodology (i.e., same inclusion/exclusion criteria, same rating scales, and raters who were trained at the same sessions) was used for the galantamine group and the control group without treatment from a community AD cohort. Galantamine was administered orally by random assignment (8, 16, or 24 mg/day) according to the clinically recommended 4-week dose escalation. Subjects with galantamine treatment

had safety and efficacy evaluations at baseline (week 0) and after 4, 8, 16, 24, 38, and 52 weeks, while economic data were collected at baseline and after 16, 24, 38, and 52 weeks. The community control group without treatment had safety, efficacy, and health economic evaluation at baseline (week 0) and after 24 and 52 weeks.

Written informed consent was obtained from each patient and caregiver. This study was conducted in accordance with the Declaration of Helsinki and its subsequent revisions, and was approved by ethics committees at each center.

Patients

Patients were included in the study if they were aged over 50 yr, had suffered from AD diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (6), and probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) (7), have mild to moderate AD (the Mini-Mental State Examination [MMSE] [8] scores of 10 to 22; the Alzheimer's Disease Assessment Scale [9]; and 11-item cognitive subscale [ADAS-cog/11] score ≥ 14), had a history of cognitive decline with a gradual onset of symptoms and progression over 6 months or more before baseline, and had responsible caregivers who would be able to provide necessary information about the patient. Patients were excluded if they had evidence of any neurodegenerative disorder other than AD; primary dementia of vascular origin, and secondary dementia caused by inflammatory diseases, infections, intoxication, metabolic diseases, or tumors.

Outcome measures

Demographic and clinical data were measured as outcomes that might influence the costs of caring for AD patients who live at home: all the following outcomes were used as independent variables in primary statistical analyses: 1) demographic and socio-economic characteristics of patients and caregivers; 2) AD characteristics (e.g., time since diagnosis of cognitive abnormality); 3) group (the galantamine group vs. the community control group); 4) functional decline assessed using the Disability Assessment for Dementia (DAD) scale, Korean version (10, 11). The 40-item DAD, based on interviews with the caregiver, measures basic activities of daily living (ADLs) (BADLs) and instrumental ADLs (IADLs), as well as the specific components required for the completion of each ADL (initiation, planning and organization, and effective performance); scores range from 0 to 100. A higher score indicates a better functional capacity; 5) cognitive impairment assessed using the ADAS-cog/11, Korean version (9, 12). A higher score indicates worse cognitive function; 6) behavioral disturbance assessed using the Behavior Patholo-

gy in Alzheimer's disease Rating Scale, Korean version (BEHAVE-AD) (13, 14). A higher score indicates more frequent and/or more serious behavioral disturbances; 7) severity of AD assessed using the Global Deterioration Scale (GDS) (15). A higher stage indicates more advanced state of AD.

Costs

Data on the resource use of all medical and other community service were collected prospectively for each patient. Resource use was measured using the adapted version of the Client Service Receipt Inventory (CSRI) (16). Primary caregivers were asked to provide details of services and costs that patients had used during the previous 2 months, which was deemed to allow for relatively accurate recall and also to be representative of service use, by face-to-face interview. Resources used included hospital and primary care services (inpatient, out-patient, 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 assessed using the caregiver time section of the Resource Utilization in Dementia (RUD) questionnaire (17). Informal caregiver time was valued at the 2002 average household help wage in Korea, equivalent to Korean Won (KRW) 6,250 (US dollar [USD] 5.22) per hour (18). The total costs were calculated by adding each cost for resource used by each patient. Unit costs for the year of 2002 are obtained from nationwide sources in Korea (19-22). All unit costs are reported in 2002 values using wage and price indices from national statistics offices or the consumer price index.

Economic evaluation

The analysis was performed from a societal perspective. The primary economic analytical technique initially used was a cost-consequence analysis with a list of multiple, clinically important between-group differences in costs and outcomes. The intent-to-treat population was used in the analyses. Costs are given in KRW and USD using a conversion rate of 1,196.5, the mean value of the fiscal year of 2002. No discounting was necessary, since the economic evaluation had a time horizon of 1 yr.

Sensitivity analysis

The following sensitivity analyses were conducted. First, to account for patients withdrawing from the study prematurely, the conventional last-observation-carried-forward (LOCF)

approach was supposed to impute missing values instead of advanced statistical methods using the mixed model or generalized estimating equation (GEE) regression analyses for this study. Second, the effects of caregiver time on costs were tested by the use of an alternative cost per hour (-50% to +50%) instead of KRW 6,250 (USD 5.22) per hour.

Statistical analysis

Univariate analyses were used to calculate the basic statistics of all variables and to test the normality of dependent variables. Statistical comparisons were performed for the galantamine group versus the control group using one-way analysis of variance (ANOVA) for continuous variables and the Cochran-Mantel-Haenszel test for categorical variables.

For the analysis of the caregiver time, a maximum of 16 hr/day was allowed for each subject for one's baseline time. The same rule was applied to the assessment of time spent caring for disabled function at 24 and 52 weeks. We supposed that at least 8 hr should be used for caregiver's personal ADL. Where values of more than 16 hr/day were recorded for caregiver time, a truncation to 16 hr/day was assigned in the analysis. To test the statistical significance of sequential changes, we conducted multivariate analyses (applying a mixed model for continuous dependent variables [i.e., caregiver time, and DAD-K]) by using the following independent variables as covariates: times of repeated assessment (0, 4, 8, 16, 24, 38, and 52 weeks), dose (0, 8, 16, and 24 mg) and individual indicators (e.g., patient and caregiver age, duration of formal education, and functional capacity).

Due to the skewed distribution of cost data, a generalized linear model using the GEE method for non-normal distribution (gamma distribution) was used when including cost data. All statistical analyses were two-sided and performed at the 0.05 significance level.

RESULTS

### Patient and caregiver characteristics at baseline (Table 1)

The mean age of patients (N=138) who were included in the 52-week study was 75.5 (SD=8.5) yr [galantamine group 74.0 (SD=8.2) yr; control group 76.8 (SD=8.5) yr] and 75.4 % were female. The mean duration of formal education was 4.0 (SD=4.6) yr [galantamine group 6.0 (SD=5.0) yr; control group 1.8 (SD=2.8) yr]. The mean time since diagnosis of cognitive abnormality was 3.3 (SD=2.9) yr [galantamine group 3.0 (SD=1.9) yr; control group 3.7 (SD=3.8) yr]. Patients in the two groups were comparable with respect to gender distribution, time since diagnosis of cognitive abnormality, the total MMSE score, and the severity of dementia assessed using the GDS. There were imbalances in age and duration of formal education of two groups. Patients in the galantamine group were more like to be younger (p=0.0272) and more educated (p<0.0001). While caregivers (N=138) in the two groups were comparable with respect to gender distribution, caregivers in the galantamine group were more likely to be younger (p<0.0001) [galantamine group 49.4 (SD=13.9) yr; control group 63.2 (SD=12.5) yr]. Therefore, all the significantly different patient and caregiver characteristics were included in the statistical models to assess any

Table 1. Baseline demographic and clinical characteristics of two study populations

Case	16-Week Comparison (n=300)			52-Week Comparison (n=138)		
	Characteristics (n=234)	Control (n=66)	$p^{†}$	Characteristics (n=72)	Control (n=66)	$p^{†}$
Patients						
Women, n (%)	178 (76.1%)	50 (75.6%)	0.9854	54 (75.0%)	50 (75.8%)	0.9181
Age (yr)	74.6±7.4	76.8±8.5	0.0201	74.0±8.2	76.8±8.5	0.0272
Duration of formal education (yr)	5.5±4.4	1.8±2.8	<0.0001	6.0±5.0	1.8±2.8	<0.0001
Time since diagnosis of cognitive abnormality (yr)	3.1±2.1	3.7±3.8	0.1041	3.0±1.9	3.7±3.8	0.1875
Total MMSE score	16.4±3.3	15.4±3.9	0.0520	16.3±3.4	15.4±3.9	0.1515
Global Deterioration Scale (GDS), n (%)*			0.2734			0.7983
Stage 4	156 (67.0%)	43 (66.2%)		42 (59.2%)	43 (66.2%)	
Stage 5	48 (20.6%)	8 (12.3%)		15 (21.1%)	8 (12.3%)	
Stage 6	29 (12.4%)	13 (20.0%)		14 (19.7%)	13 (20.0%)	
Stage 7	0	1 (1.5%)		0	1 (1.5%)	
Caregivers						
Women, n (%)	152 (65.0%)	39 (59.1%)	0.3823	44 (61.1%)	39 (59.1%)	0.8094
Age (yr)	51.4±13.9	63.2±12.5	<0.0001	49.4±13.9	63.2±12.5	<0.0001

Values are expressed as mean [standard deviation] unless otherwise indicated.

MMSE, mini-mental state examination. *Data in the variable GDS has two missing information (N=298), one for each group; †data were analyzed between the community clinical trial group and the naturalistic community study group by means of one-way analysis of variance, except for gender and GDS (chi-square test).

Caregiver time of for basic ADLs (hr/month)

Caregiver time for instrumental ADLs (hr/month)
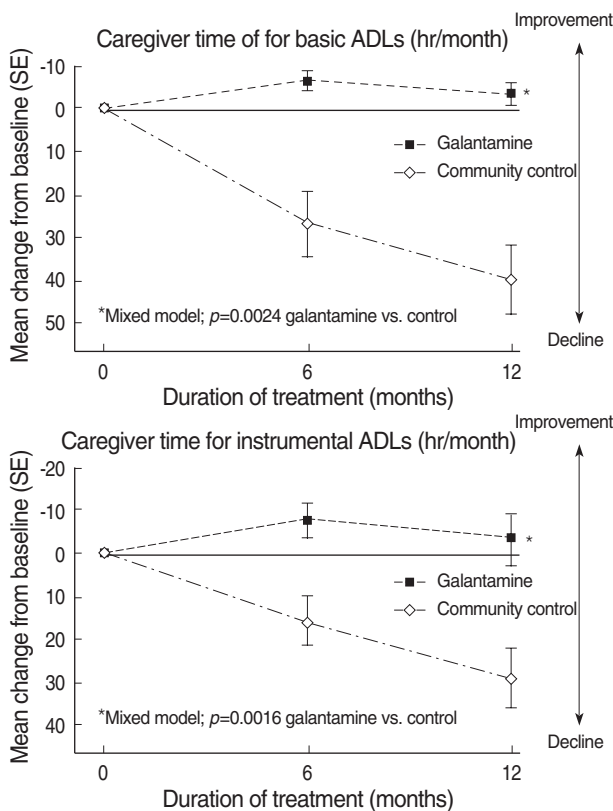
Patients evaluated (n)

Months	0	6	12
Galantamine	72	48	37
Community control	66	60	45

Fig. 1. Mean change (standard error) over time from baseline in caregiver time spent caring for disabled function.

effect on the dependent variables.

These statistics were not different when applied to the subjects of original clinical trial (N=300) (Table 1). Baseline characteristics of patients and caregivers were not statistically significantly different between two galantamine groups of original 16-week clinical trial (n=234) and the 52-week trial (n=72).

Clinical efficacy

After 52 weeks of treatment, results of mixed model analyses showed significantly reduced caregiver times caring for BADLs and IADLs in the galantamine group, relative to baseline (BADLs, F=24.63, $p<0.0001$; IADLs, F=14.84, $p<0.0001$) and compared with the control group (BADLs, F=9.62, $p=0.0024$; IADLs, F=10.51, $p=0.0016$) (Fig. 1). The mean reduction in the caregiver time caring for BADLs from baseline were 3.4 hr per month for the galantamine group, whereas the subjects in the community control group required an average of 39.6 more hour of caregiver time per month

(Fig. 1). It means that the 52-week galantamine treatment can save 85 min per day in caring for BADLs when compared to no treatment. The mean reduction in the caregiver time caring for IADLs from baseline were 3.3 hr per month for the galantamine group, whereas subjects in the community control group required an average of 29.2 more hours of caregiver time per month (Fig. 1). It means that the 52-week galantamine treatment can save 64 min per day in caring for IADLs when compared to no treatment. At the end of 52 weeks, caregiver time for BADLs and IADLs in the galantamine group was reduced 6.7 hr per month, whereas it increased by 68.8 hr per month in the community control group compared to baseline (F=10.01, $p=0.0019$). It means that the 52-week galantamine treatment can save 149 min per day in caring for both BADLs and IADLs when compared to no treatment.

After 52 weeks of treatment, results of a mixed model analysis of the mean total score of DAD-K showed improved functional capacity in the galantamine group, relative to baseline (F=13.89, $p<0.0001$) and compared with the control group (F=16.89, $p<0.0001$). The mean improvement from baseline was 6.1 points for the galantamine group, whereas the community control group deteriorated by a mean of 17.4 points (Fig. 2). Similarly, statistically significant improvement in mean BADLs score of the DAD-K was also observed in galantamine groups after 52 weeks, relative to baseline (F=7.61, $p<0.0001$) and compared with the control group (F=5.05, $p=0.0262$). The mean BADLs score improvement in the galantamine group was 0.8 points, whereas the control group's score deteriorated by a mean of 14.8 points. The mean IADLs score of the DAD-K was also statistically significantly improved in the galantamine group after 52 weeks, relative to baseline (F=9.61, $p<0.0001$) and compared with the control group (F=14.11, $p<0.0001$). The mean IADLs score improvement in the galantamine group was 10.1 points, whereas the control group's score deteriorated by a mean of 19.3 points.

After 52 weeks of treatment, results of a mixed model analysis of the ADAScog/11K showed improved cognitive function in the galantamine group, relative to baseline (F=44.54, $p<0.0001$) and compared with the control group (F=36.61, $p<0.0001$). The mean improvement from baseline was 4.5 points for the galantamine group, whereas the community control group deteriorated by a mean of 14.3 points.

After 52 weeks of treatment, results of a mixed model analysis showed improved behavior measured by the BEHAVE-AD in the galantamine group, relative to baseline (F=33.89, $p<0.0001$) and compared with the control group (F=21.28, $p<0.0001$).

However, the result of a mixed model analysis did not showed a between-group (F=1.88, $p=0.1355$) or between-time difference (F=1.68, $p=0.1952$) in severity of dementia measured by the GDS.
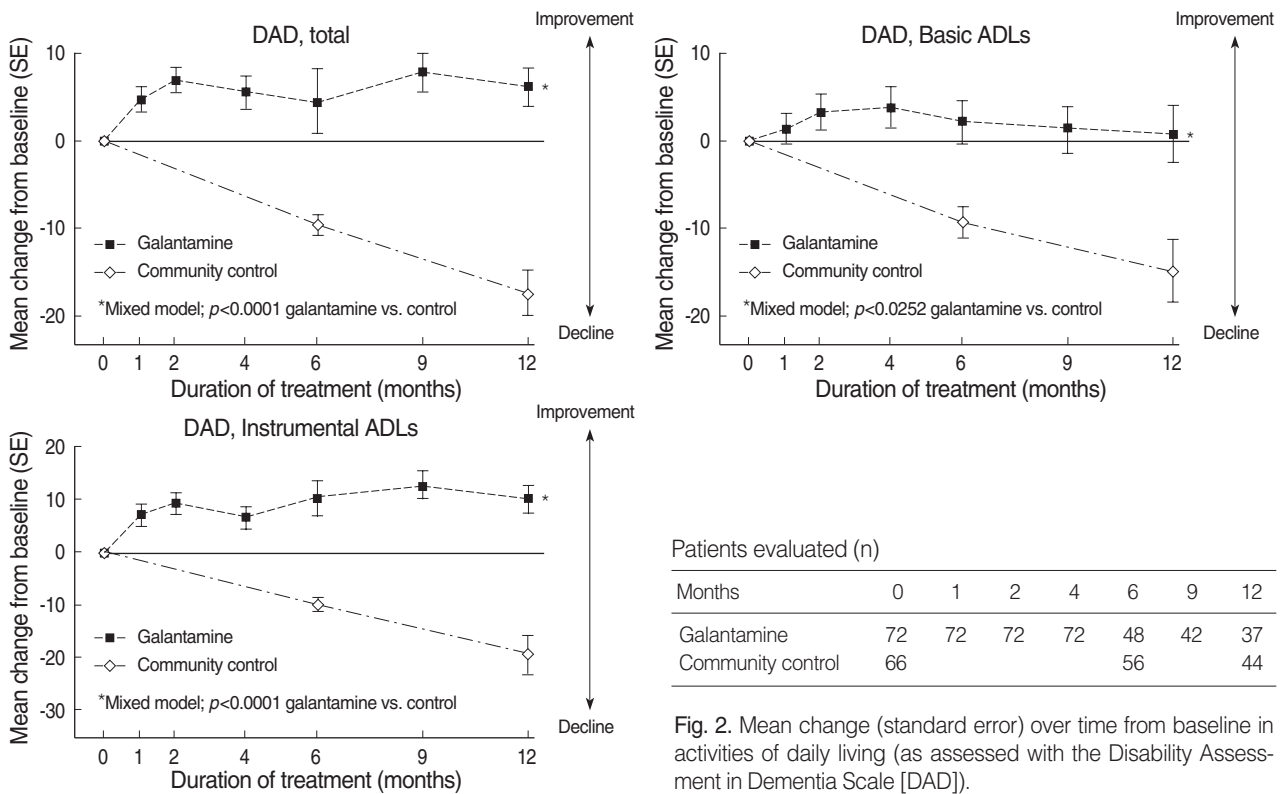
Fig. 2. Mean change (standard error) over time from baseline in activities of daily living (as assessed with the Disability Assessment in Dementia Scale [DAD]).

Table 2. Costs of the long-term 52 week study population

Characteristics	Galantamine			Control			Cost saving[†]	$p^{‡}$
	Baseline (n=72)	Week 52 (n=45)	$\triangle^{*}$	Baseline (n=66)	Week 52 (n=45)	$\triangle^{*}$		
Direct costs	6,522±3,083	9,159±3,566	+2,637	6,460±4,264	6,445±3,990	-15	-2,652	0.6404
Trial medication	0	1,465±503	+1,465	0	0	0	-1,465	-
Health care service	1,576±1,038	1,944±643	+368	213±293	358±400	+145	-223	0.0685
Social care service	329±1,601	1,055±2,726	+726	333±945	401±956	+68	-658	0.2882
Out-of-pocket support	703±2,404	877±1,826	+174	1,464±3,867	1,213±3,167	-251	-425	0.0889
Accommodation	3,915±728	3,818±658	-97	4,449±845	4,473±824	+24	+121	0.0015
Indirect costs	5,428±6,411	3,157±6,699	-2,271	8,970±11,260	14,721±16,323	+5,751	+7,992	0.0004
Caregiver patient care	5,218±6,210	2,806±6,613	-2,412	6,733±9,172	11,854±13,899	+5,121	+7,533	0.0054
Missed work	210±1,218	351±1,490	+141	2,237±3,237	2,867±3,934	+630	+489	0.0414
Total costs	11,950±7,428	12,315±8,557	+365	15,429±12,795	21,166±17,470	+5,737	+5,372	0.0089

Values [USD] are expressed as mean±standard deviation unless otherwise indicated.

All the costs in this table are presented after conversion to 52-week costs by multiplying 6 to 2-month costs.

[*]$\triangle$, mean at week 52 mean at baseline; [†]Cost saving, change from baseline in the control group at week 52-change from baseline in the galantamine group at week 52. A positive value indicates saving with galantamine. Monetary values are expressed as US dollars; [‡]the GEE model was used to test statistical significance between 2 groups in this longitudinal data analysis, using statistically different baseline characteristics as covariates (i.e., patient age, caregiver age, and duration of formal education) and non-normal distribution (gamma distribution) for costs.

Total costs

Grossly two areas of costs were investigated: direct cost (trial medication, health care costs, social care costs, out-of-pocket support paid by patients or caregivers, and accommodation) and indirect costs (informal care and missed work of caregiver). Direct costs and indirect costs were added together to give a total cost. The total costs and their standard deviations (SDs) per patient after 52 weeks were KRW 14,735,000 ±10,238,000 (USD 12,315±8,557) for the galantamine group and KRW 25,325,000±20,903,000 (USD 21,166 ±17,470) for the control group (Table 2). Cost saving for

galantamine treatment after 52 weeks compared with the control group who had not taken galantamine during the 52-week study period (cost saving=change from baseline in control group-change from baseline in the galantamine group), can be estimated KRW 6,428,000±3,068,000 (USD 5,372 ±2,564). This 52-week total cost saving was statistically significantly different between the two groups when baseline differences were adjusted (GEE: p=0.0089).

Direct costs

Direct costs were provided for all patients. Mean direct costs and their SDs after 52 weeks for the galantamine group were KRW 10,959,000±4,267,000 (USD 9,159±3,566) per patient compared with KRW 7,711,000±4,773,000 (USD 6,445±3,990) per patient for the control group, resulting in an additional cost per patient of KRW 3,173,000± 3,493,000 (USD 2,652±2,919) (GEE; p=0.6404) (Table 2). Following subcategory costs in the galantamine group increased direct costs after 52 weeks; trial medication (KRW 1,753,000; USD 1,465), health care service (KRW 440,000; USD 368), social care services (KRW 869,000; USD 726), and out-of-pocket support (KRW 208,000; USD 174), while accommodation cost in the galantamine group was significantly decreased when compared to the control group (GEE; p=0.0015) (Table 2). During the 2nd half of the 52-week study, direct costs in the galantamine group were increased (△=+USD 781), while those in the control group were decreased (△=−USD 931) (GEE; p<0.0001). Death of 14 patients who had used high costs in the control group contributed to the widened gap in the direct costs (GEE; p<0.0001).

Indirect costs

Indirect costs were time-related in this study; time for caring for the AD patients and time for missed work of the caregiver. Indirect costs after 52 weeks for the galantamine group were KRW 3,778,000±8,015,000 (USD 3,157±6,699) per patient compared with KRW 17,614,000±19,530,000 (USD 14,721±16,322) per patient for the control group. Adjusted cost saving was KRW 9,562,000±4,117,000 (USD 7,992±3,441) per patient for indirect costs (GEE; p= 0.0004) (Table 2).

Sensitivity analyses

When costs were imputed for patients withdrawing from the study prematurely (LOCF approach), the total cost after 52 weeks were KRW 14,297,000 (USD 11,949) for the galantamine group and KRW 23,085,000 (USD 19,294) for the control group. Adjusted cost saving for the galantamine treatment after 52 weeks compared with the control group was estimated KRW 4,626,000 (USD 3,866). This 52-week total cost saving was statistically significantly different between

two groups (GEE: p=0.0007). Direct costs after 52 weeks for the galantamine group were KRW 9,248,000 (USD 7,729) per patient compared with KRW 8,137,000 (USD 6,800) per patient for the control group, resulting in an additional cost per patient of KRW 1,036,000 (USD 866) (GEE; p= 0.2336). Indirect costs after 52 weeks for the galantamine group were KRW 5,049,000 (USD 4,219) per patient compared with KRW 14,948,000 (USD 12,493) per patient for the control group. Adjusted cost saving was KRW 5,662,000 (USD 4,732) per patient for indirect costs (GEE; p<0.0001).

When we tested a range of unit cost of caring for a patient per hour (-50% to +50% of KRW 6,250 [USD 5.22] per hour), cost saving in total costs ranges from KRW 4,056,000 to 15,095,000 (USD 3,390 to 12,616) and cost saving in indirect costs ranges from KRW 5,092,000 to 16,131,000 (USD 4,256 to 13,482). The magnitude of the difference in costs obtained in these sensitivity analyses differed in the main analyses, but the direction of the results did not alter. These sensitivity analyses, therefore, confirmed the findings of the main economic evaluation.

DISCUSSION

A 16-week trial of galantamine had demonstrated a superior efficacy relative to baseline and compared with the control group in the treatment of patients with mild to moderate AD in a Korean population (5). The 52-week prospective study also demonstrated significant clinical improvements relative to baseline and compared with the control group. Results for the galantamine group was consistently and statistically significantly superior to the control group. This study extends the result of previous randomized studies that also showed beneficial effects of galantamine (5, 23-26). Reduction in time caring for the patients and improvement in functional capacity maintained during the 52-week study period in the galantamine group, whereas greatly increased caregiver time and progressive functional deteriorations were observed in the control group. Difference in caregiver time between two groups was equivalent to 9.4 (=[6.7 +68.8] hr/8 hr) working days per month or 112.8 working days per year under the assumption that a person works 8 hr a day (Fig. 1). Economic analyses of the 52-week prospective study indicate that galantamine could reduce the overall cost of caring for AD patients. When compared to no treatment, estimated cost saving of galantamine treatment in total cost averages KRW 6,428,000 (USD 5,372) per patient a year (GEE, p=0.0089), while estimated additional, not statistically significant, direct costs average KRW 3,173,000 (USD 2,652) per patient a year (GEE, p=0.6404).

Loss of autonomy due to disabled BADLs and IADLs is an important determinant of quality of life and caregiver burden. More rapid decline in IADLs was observed in moderate AD than in mild AD, whereas basic ADLs were lost more

rapidly in severe AD (27). As informal (unpaid) caregivers have performed most of the care for patients with dementia in Korea and soon they will inevitably place their relatives in institutional care, valuing these efforts is an important issue. The measurement and valuation of time spent caring for patients with dementia pose a great challenge. In this study, the amount of time spent caring for disabled BADLs and IADLs were converted to part of indirect cost using a replacement cost approach. It should not be considered that family care is a cost-free alternative to institutional care. Instead, caregivers incur huge care burdens, including economic hardship, curtailment of social activities, emotional strain, and psychological distress (28).

Clinical trials give necessary but not sufficient information for judging the cost effectiveness of new treatment in dementia. Drug efficacy data need to be combined with epidemiologic data that describe the natural progression of the disease, with economic data to quantify resource use and costs, and possibly also with quality-of-life data to estimate the benefits of treatment to patients and to caregivers (29). This study has a merit that epidemiologic data for natural progression had been included, so that all these results are more appropriate for pharmacoeconomic analyses.

Direct costs in the galantamine group increased constantly through 52 weeks, while that in the control group mostly remained unchanged. In the galantamine group, reduced indirect costs offset the cost of trial medication (Table 2). If this study had been performed in a society where better and sufficient health and social care services for AD patients could have been provided, cost of galantamine should have been offset by reduced direct costs in health and social care service like in previous studies (30, 31). In 2002, health and social care services in Korea were greatly deficient. The institutional care capacity rate in Korea was 30% in 2003 (personal communication; Ministry of Health and Welfare). Therefore, all these services were provided on a 'first come, first served' basis. After study entry, patients in the galantamine group began to use more health care services, more social care services, and spent more on out-of-pocket expenses, whereas patients and caregivers in the control group had done fewer efforts to receive more health and social care services and even reduced out-of-pocket expenses. Patients and caregivers of the galantamine group had regularly visited memory clinics for study interview and trial medication, while, in the control group, research psychologists visited patient's home to complete the study interview. Further, patients and caregivers in the galantamine group were willing to take medical treatment of AD, but those in the control group were not. These different health behaviors and attitude appear to make two groups greatly different.

There are some limitations in this study. Firstly, as for any clinical trials, the inclusion/exclusion criteria may limit the ability to extrapolate the results of this study to the general population. Secondly, using study design without a placebo

group. baseline characteristics were different in the galantamine group and the control group. To adjust for the baseline difference, cost savings were calculated using mean difference from week 52 to baseline and all the significantly different patient and caregiver characteristics were included in the statistical models to assess any effect on the dependent variables. However, this limitation requires careful attention to the methods employed in nonrandomized control studies (32) and suggests that all results of such studies should be considered in the light of data from relevantly controlled trials. Thirdly, dropout rates were high in both groups during 52-week study. A total of 138 patients enrolled in the trial, 37 (51%) of the galantamine group and 45 (68%) of the control group completed the 52-week prospective study. Of 35 patients of the galantamine group who did not respond to the final study interview at the 52-week study, 15 did not visit without comments (but not dead or institutionalized), 2 hospitalized, 3 moved, and 15 refused to interview. Of the 21 patients in the control group who did not complete the 52-week study, 14 were dead, 2 institutionalized, 3 absent during community survey period (n=3), and 2 refused the interview. Although there was no statistically significant different demographic, clinical, and cost profiles between those who completed and those who dropped out, this limitation requires careful attention when we interpret results of this study because those who dropped out might possibly cost much more or much less than expected in case that they remained to the end of the trial. Fourthly, the range of the MMSE score (10 to 22) for recruitment criteria was not wide enough to present study results according to the different stage of dementia (i.e., mild, moderate). Further studies need to be performed to make these results more useful for policy decision makers.

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