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The efficacy of galantamine in the treatment of Alzheimer's disease: comparison of patients previously treated with acetylcholinesterase inhibitors to patients with no prior exposure

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SUMMARY

Background Acetylcholinesterase inhibitors (AChEIs) can provide benefits at the cognitive, behavioral, and functional levels to patients with Alzheimer's disease (AD). With more AChEIs now available, treatment considerations may include whether the patient has had prior exposure to an AChEI.
Objective To compare the effects of galantamine in patients with AD who were previously exposed to AChEIs with its effects in patients with AD who had no previous exposure, using a *post hoc* analysis.
Results Patients in groups treated with galantamine 16 mg/day and 24 mg/day achieved statistically significant improvements in ADAS-cog/11 scores in comparison with those who received placebo (naive: $p = 0.003$ and 0.005, respectively; prior exposure: $p < 0.001$ and 0.001, respectively). Similarly, a greater number of patients treated with galantamine 16 mg/day and 24 mg/day exhibited no change or improvement in their CIBIC-plus scores compared to patients who received placebo (naive: $p < 0.001$ and $p = 0.077$, respectively; prior exposure: $p = 0.005$ and $p = 0.001$, respectively). There were no significant differences in adverse events between naive patients and those with prior exposure to AChEIs.
Conclusions Galantamine is effective and safe in patients with AD, regardless of previous exposure to AChEIs. Copyright © 2003 John Wiley & Sons, Ltd.

KEY WORDS — galantamine; efficacy; acetylcholinesterase inhibitors; Alzheimer's disease

INTRODUCTION

The loss of cholinergic neurotransmission in the cerebral cortex, hippocampus, and other areas of the brain is thought to contribute to the progressive declines in cognition, ability to perform activities of daily living, and behavior in patients with Alzheimer's disease (AD) (Nordberg *et al.*, 1989; Francis *et al.*, 1999). Currently approved treatments for AD inhibit degradation of acetylcholine by the enzyme acetylcholinesterase (AChE). These drugs, collectively referred to as acetylcholinesterase inhibitors (AChEIs), increase the availability of acetylcholine in the synaptic cleft (Francis *et al.*, 1999) and have been shown to provide benefits at the behavioral, cognitive, and/or functional levels (Kaufer *et al.*, 1996; Rogers *et al.*, 1998; Mega *et al.*, 1999; Rosler *et al.*, 1999; Raskind *et al.*, 2000; Tariot *et al.*, 2000).

In the USA, four AChEIs have been approved for the treatment of symptoms of mild-to-moderate AD: tacrine, donepezil, rivastigmine, and galantamine (Nordberg and Svensson, 1998; Francis *et al.*, 1999). Given the aging of our population and subsequent increase in the number of people older than 65 years of age who are diagnosed with AD, there is an

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increased probability of patients being exposed to AChEIs. Because of the observed difficulties in the assessment of treatment success with these drugs, many patients and caregivers become discouraged when patient improvement is not observed or maintained. In addition, cholinergic side effects may develop. Thus, perceived inefficacy or side-effect issues may lead to the discontinuation of treatment.

For example, two independent studies have shown that, over one year of treatment, patients receiving donepezil have a typical length of therapy of between 133 days (NDC Health Retail Pharmacy Database, 2001) and 169 days (Malkin *et al.*, 2001). In clinical practice, physicians are frequently confronted with deciding whether to implement cholinergic therapy in a patient who may have been exposed previously to a cholinesterase inhibitor. Unfortunately, to date there has been no available information to guide the physician in making this important decision. The goals of this *post hoc* analysis of a previously conducted clinical trial (Tariot *et al.*, 2000) were to address this issue by comparing the efficacy and safety of galantamine in patients with AD previously treated with cholinesterase inhibitors with those in patients naive to such treatment.

METHODS

Patients

Inclusion and exclusion criteria and patient baseline demographics were described previously in the original study by Tariot and colleagues (Tariot *et al.*, 2000). Briefly, patients who entered the study were assessed as having probable AD in accordance with the National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association criteria. Mild-to-moderate dementia was defined as a score of 10–22 on the Mini-Mental State Examination (MMSE) and a score of at least 18 on the Alzheimer's Disease Assessment Scale/11-item cognitive subscale (ADAS-cog/11). Patients taking AChEIs prior to the study were required to stop therapy for at least 60 days prior to study entry to achieve optimal washout. For demographic information and baseline characteristics of the entire study population, see Table 1.

Post hoc analysis

The original study was a 5-month, multicenter, placebo-controlled, double-blind trial conducted in the United States to study the efficacy and safety of galantamine in patients with mild-to-moderate AD ($n = 978$) (Tariot *et al.*, 2000). Briefly, there were four parallel treatment groups (placebo, galantamine 8 mg/day, 16 mg/day, and 24 mg/day), in which patients were distributed in a ratio of 2:1:2:2. Target doses of galantamine were reached using a 4-week dose-escalation schedule.

Efficacy was measured using the ADAS-cog/11 and the Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC-plus). These assessments were performed at baseline and Month 5. Safety and tolerability were assessed by monitoring vital signs and adverse events. Physical examinations, electrocardiograms, and standard laboratory tests were also used to evaluate the safety and tolerability of galantamine. To perform this *post hoc* analysis, efficacy and safety data from patients in each treatment group of the original study (Tariot *et al.*, 2000) were stratified according to prior exposure to AChEIs.

Previous use of AChEIs was recorded in the case record forms (although information regarding the length of therapy and the specific agent[s] to which patients were exposed was not captured). A 60-day cholinomimetic-free period was required prior to randomization.

Statistical analysis

Statistical comparisons were performed for each treatment group versus placebo. The changes in ADAS-cog/11 scores between the treatment and placebo groups were compared with a two-way analysis of variance (ANOVA). The changes in CIBIC-plus scores of the treatment groups with placebo were compared using the generalized Cochran-Mantel-Haenszel (CMH) test for categorical variables. Statistical significance was set at alpha <0.05. All statistical analyses were performed using standard statistical software (SAS Institute, Cary, NC).

RESULTS

Distribution of patients with and without prior use of AChEIs

A total of 446 patients (45.6% of the study population) with prior use of AChEIs were represented in the four treatment groups: (1) 127, placebo; (2) 60, galantamine 8 mg/day; (3) 141, galantamine 16 mg/day; and (4) 118, galantamine 24 mg/day. A total of 532 naive patients (54.4% of the study population) were represented in the four treatment groups: (1)

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Table 1. Demographic and baseline disease characteristics for all patients

Characteristics	Placebo ($n = 286$)	GAL 8 mg ($n = 140$)	GAL 16 mg ($n = 279$)	GAL 24 mg ($n = 273$)
Sex: *n* (%)				
Male	108 (37.8%)	50 (35.7%)	105 (37.6%)	90 (33.0%)
Female	178 (62.2%)	90 (64.3%)	174 (62.4%)	183 (67.0%)
Race: *n* (%)				
Caucasian	267 (93.4%)	132 (94.3%)	260 (93.2%)	249 (91.2%)
Black	13 (4.5%)	5 (3.6%)	12 (4.3%)	14 (5.1%)
Hispanic	3 (1.0%)	3 (2.1%)	5 (1.8%)	4 (1.5%)
Oriental	3 (1.0%)	0 (0.0%)	1 (0.4%)	3 (1.1%)
Other	0 (0.0%)	0 (0.0%)	1 (0.4%)	3 (1.1%)
Age, y (mean ± SE)	77.1 ± 0.46	76 ± 0.61	76.3 ± 0.49	77.7 ± 0.43
Weights, kg (mean ± SE)	67.55 ± 0.835	69.88 ± 1.413	68.12 ± 0.867	66.55 ± 0.803
Smoker—Yes: *n* (%)	15 (5.2%)	6 (4.3%)	15 (5.4%)	11 (4.0%)
Age at onset of cognitive problems, y (mean ± SE)[a]	73.2 ± 0.49	72.3 ± 0.64	72.6 ± 0.5	74.2 ± 0.47
Years since cognitive problem diagnosis (mean ± SE)	4.33 ± 0.152	4.14 ± 0.212	4.22 ± 0.164	3.92 ± 0.164
Age at diagnosis of probable AD, y (mean ± SE)	76.1 ± 0.47	75.2 ± 0.63	75.4 ± 0.5	76.8 ± 0.44
Years of AD diagnosis (mean ± SE)	1.42 ± 0.104	1.26 ± 0.122	1.42 ± 0.11	1.32 ± 0.108
First-degree relative(s) with AD: *n* (%)	74 (25.9%)	41 (29.5%)	83 (30.0%)	76 (27.8%)
Previously taken cholinomimetic agent: *n* (%)	127 (44.4%)	60 (42.9%)	141 (50.5%)	118 (43.2%)
Total MMSE score (mean ± SE)	17.7 ± 0.21	18 ± 0.3	17.8 ± 0.21	17.7 ± 0.23
ADAS-cog/11 score at baseline (mean ± SE)	29.4 ± 0.63	27.8 ± 0.94	29.4 ± 0.66	29.0 ± 0.67
APOE type: *n* (%)				
2–2/2–3/3–3	90 (35.3%)	48 (37.5%)	112 (44.1%)	88 (35.5%)
2–4/3–4	133 (52.2%)	64 (50.0%)	105 (41.3%)	131 (52.8%)
4–4	32 (12.5%)	16 (12.5%)	37 (14.6%)	29 (11.7%)

Adapted from Tariot, 2000.
[a]Difference between treatment groups from ANOVA model with treatment and new investigator as factors.

159, placebo; (2) 80, galantamine 8 mg/day; (3) 138, galantamine 16 mg/day; and (4) 155, galantamine 24 mg/day.

Efficacy

The ADAS-cog/11 scores for patients previously exposed or naive to AChEIs are presented in Table 2. In both subpopulations, patients treated with galantamine 16 mg/day and 24 mg/day achieved statistically significant improvements in cognitive function compared with placebo (naive: $p = 0.003$ and $p = 0.005$, respectively; prior exposure: $p < 0.001$ and $p < 0.001$, respectively). Previously exposed patients had higher baseline ADAS-cog/11 scores than naive patients, suggesting that previously exposed patients had more severe disease at study entry. Although ADAS-cog/11 scores among patients treated with galantamine 8 mg/day and those treated with placebo were numerically different in both previously exposed patients and naive patients, the differences were not statistically significant. In the placebo group, previously exposed patients also showed a greater change from baseline (2.7 points) in ADAS-cog/11 scores at 5 months than naive patients (0.9 points). Improvements from baseline in ADAS-cog/11 scores were seen in both subpopulations treated with galantamine 16 mg/day and 24 mg/day (Figure 1).

For patients with previous exposure to AChEIs, 56.9% and 60.8% of those treated with galantamine 16 mg/day and 24 mg/day, respectively, demonstrated an improvement in CIBIC-plus scores (Table 2). These percentages were 19% and 23% greater than for placebo (38.3%) ($p = 0.005$ and $p = 0.001$, respectively). For naive patients, 78.6% and 67.0% of those treated with galantamine 16 mg/day and 24 mg/day, respectively, demonstrated improvement or no change in CIBIC-plus scores. These percentages

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Table 2. Assessment of cognitive and global function

Group	ADAS-cog/11					CIBIC-plus			
		Mean (SE)			Comparison with placebo[a]		Number of patients (%) with improvement or no change	Comparison with placebo[b]	
	n	Baseline	Month 5	Δ	*p*-value	*n*		Δ%	*p*-value
Previously exposed to AChEIs									
Placebo	109	31.4 (1.02)	34.1 (1.24)	2.7 (0.63)	—	115	44 (38.3)	—	—
8 mg/day[c]	49	28.4 (1.55)	29.6 (1.61)	1.2 (0.74)	0.180	49	22 (44.9)	6.6	0.429
16 mg/day[c]	106	29.8 (1.01)	28.9 (1.14)	−0.8 (0.54)	<0.001	109	62 (56.9)	18.6	0.005
24 mg/day[c]	96	30.4 (1.10)	28.7 (1.27)	−1.8 (0.68)	<0.001	97	59 (60.8)	22.5	0.001
Naïve to AChEIs									
Placebo	116	25.8 (0.82)	26.7 (1.06)	0.9 (0.58)	—	122	68 (55.7)	—	—
8 mg/day[c]	52	26.0 (1.42)	25.1 (1.51)	−0.9 (0.87)	0.360	57	32 (56.1)	0.4	0.960
16 mg/day[c]	102	27.0 (1.06)	24.9 (1.23)	−2.1 (0.58)	0.003	103	81 (78.6)	22.9	<0.001
24 mg/day[c]	115	26.9 (0.92)	25.1 (0.96)	−1.9 (0.57)	0.005	115	77 (67.0)	11.3	0.077

[a]Two-way ANOVA with treatment and investigator as factors.
[b]CMH test controlling for investigator effect.
[c]Dose of galantamine.

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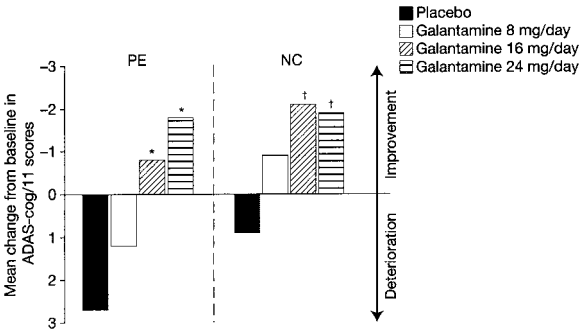

Figure 1. Mean change from baseline in ADAS-cog/11 scores. Definitions: PE = previously exposed to cholinesterase inhibitors; NC = naive to cholinesterase inhibitors. $^{*}p \leq 0.001$ *vs* placebo; $^{\dagger}p \leq 0.005$ *vs* placebo

were 23% and 11% greater than for placebo (55.7%) ($p < 0.001$ and $p = 0.077$, respectively). The numerical response for naive patients receiving galantamine 24 mg/day was not statistically significant, which may be due to the size of this subpopulation, the sensitivity of the CIBIC-plus, or more mild disease in this group of patients.

Safety

There were no significant differences in adverse events reported between patients with or without prior cholinesterase inhibitor exposure. The percentages of patients experiencing nausea, vomiting, weight decrease, bradycardia, fatigue, and syncope were equally represented in both subpopulations. Convulsions and muscle weakness were not prevalent in any treatment group, regardless of prior exposure to AChEIs.

Only nausea (16.5% of patients receiving 24 mg/day of galantamine *vs* 4.5% of placebo-treated patients), vomiting (9.9% of patients receiving 24 mg/day of galantamine *vs* 1.4% of placebo-treated patients), and weight decrease (5.4% of patients treated with 16 mg/day of galantamine *vs* 1.4% of placebo-treated patients) were experienced by more than 5.0% of patients in any treatment group.

CONCLUSIONS

This *post hoc* analysis is the first to evaluate the impact of prior exposure to AChEIs on current treatment with cholinomimetics. This analysis of the stratified data set from the original study by Tariot and colleagues (Tariot *et al.*, 2000) shows that there were no differences in efficacy or side effects between the two patient groups (those who were previously exposed to AChEIs and those who were AChEI naive). This post hoc analysis suggests that galantamine may be beneficial in patients who have discontinued treatment with conventional AChEIs. Thus, our data suggest that discontinuation of prior cholinesterase inhibitor treatment does not preclude the possibility of future effective treatment with galantamine.

These data do not explain whether this observed response is specific to galantamine or a broad effect of this class of compounds. Should these findings be confirmed in appropriately designed clinical trials, clinicians will be able to provide patients with AD an opportunity to benefit from the full spectrum of available treatments.

Several questions remain concerning selection of patients for the study. It is not known if patients who received previous AChEI therapy discontinued treatment due to side effects or due to lack of efficacy. Also, it is unknown if the 60-day washout period limited access to the study for some individuals. These limitations should be explored in future studies. Data were not analyzed for experienced and naive patient subgroups regarding secondary efficacy parameters.

In summary, the data analyzed for the primary efficacy parameters suggest that galantamine may be a viable treatment option in patients who have reported prior exposure to conventional AChEIs as well as for those with no previous exposure when compared with placebo. No significant differences were found between groups regarding adverse events. Further trials will be required to confirm these preliminary findings.

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