The Cognitive Benefits of Galantamine Are Sustained for at Least 36 Months

A Long-term Extension Trial

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Background: Alzheimer disease (AD) causes progressive cognitive and functional decline over years. Although cholinesterase inhibitors have demonstrated efficacy in studies lasting 3 to 6 months, little is known about long-term therapy.

Objective: To report the long-term cognitive effects of galantamine hydrobromide given continuously for 36 months in AD patients.

Participants: Subjects were 194 US patients with mild to moderate AD who had been randomized to continuous galantamine therapy in either of 2 double-blind placebo-controlled trials. Subjects subsequently received open-label continuous galantamine therapy for up to 36 months.

Main Outcome Measures: Effects on cognition were analyzed as change from study enrollment baseline in scores on the Alzheimer’s Disease Assessment Scale–11-item cognitive subscale. Cognitive decline in galantamine-treated subjects was compared with that of a clinically similar historical control sample of AD patients who had received placebo for 12 months and with the mathematically predicted decline of untreated patients over 36 months. The rate of cognitive decline of patients who completed the entire 36-month trial (n=119) was compared with that of patients who withdrew for any reason during the long-term open-label extension (n=75). An inverted responder analysis was also performed in 36-month completers.

Results: Patients treated continuously with galantamine for 36 months increased a mean±SE of 10.2±0.9 points on the Alzheimer’s Disease Assessment Scale–11-item cognitive subscale—a substantially smaller cognitive decline (approximately 50%) than that predicted for untreated patients. Patients discontinuing galantamine therapy before 36 months had declined at a similar rate before discontinuation as those completing 36 months of treatment. Almost 80% of patients who received galantamine continuously for up to 36 months seemed to demonstrate cognitive benefits compared with those predicted for untreated patients.

Conclusions: Cognitive decline over 36 months of continuous galantamine treatment was substantially less than the predicted cognitive decline of untreated patients with mild to moderate dementia. Thus, the cognitive benefits of galantamine seemed to be sustained for at least 36 months. These findings suggest that galantamine slows the clinical progression of AD.

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ALZHEIMER DISEASE (AD), the most common cause of late-life dementia, is an inexorably progressive disorder culminating over multiple years in severe disability and death. A deficit in brain cholinergic function contributes to the cognitive impairments of AD. Acetylcholinesterase inhibitors (AChEIs), which enhance cholinergic neurotransmission, improve cognition modestly in a subgroup of AD patients and stabilize cognition and function on average for up to 12 months. In several AChEI studies, patients initially randomized to receive placebo and then given open-label AChEI treatment failed to achieve the same improvement as those initially randomized to receive an AChEI who continued to undergo open-label AChEI treatment. In addition, a retrospective analysis of data from a large trial of tacrine hydrochloride in AD patients suggested that long-term treatment at an adequate dose delayed nursing home placement. These observations indicate that AChEIs may slow the clinical progression of AD. Were this to be demonstrated over multiple years, it would have substantial clinical and public health implications.

Determining the possible long-term benefits of AChEI treatment would require a multiyear placebo-controlled clinical trial. However, ethical considerations...
preclude long-term placebo use. A less direct, yet informative, approach is to determine if AD patients given an AChEi for multiple years manifest more gradual cognitive decline than would be predicted by a mathematical model derived from observations of AD patients followed up longitudinally predating the introduction of AChEIs. The equation of Stern et al.\(^4\) predicts subsequent decline among AD patients untreated with AChEIs over multiple years from a given baseline level of cognitive function as quantified by the Alzheimer’s Disease Assessment Scale–11-item cognitive subscale (ADAS-cog/11).\(^5\) Because the ADAS-cog/11 is the most common measure of cognition in AD clinical trials, it is possible to compare ADAS-cog/11 score changes observed over time in AD patients treated continuously with AChEIs with changes predicted by the equation of Stern et al.

Galantamine hydrobromide (Reminyl), the most recently approved AChEi, exhibits a dual mechanism of action: competitive acetylcholinesterase inhibition and nicotinic receptor modulation.\(^3,16,17\) In several large phase 3 clinical trials, galantamine demonstrated benefits across all domains of mild to moderate AD (cognition, activities of daily living, behavior, and caregiver burden), with a favorable tolerability and safety profile.\(^4,7\)

Herein, we compared cognitive decline in AD patients treated continuously with galantamine, 24 mg/d, for up to 36 months with the decline predicted by the equation of Stern et al.\(^4\) We also asked if any apparent slowing of decline in patients taking galantamine for 36 months could be attributed to rapid decliners being overrepresented among patients who discontinued treatment at some point during long-term open-label treatment.

### METHODS

#### SUBJECTS

Subjects met the following criteria at enrollment into the original double-blind studies: probable AD based on the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association’s criteria,\(^5\) mild to moderate dementia (score of 11-24 on the Mini-Mental State Examination),\(^6\) cognitive decline that was gradual in onset and progressive over at least 6 months, and no clinical evidence of a cause of cognitive impairment other than AD.

#### OUTCOME MEASURES

Safety evaluations included physical examinations, electrocardiography, vital sign measurements, standard laboratory tests, and adverse event (AE) monitoring.

Effects on cognition were analyzed as ADAS-cog/11 score changes from baseline at double-blind study phase enrollment to that after 36 months of continuous galantamine treatment. Subjects receiving galantamine, 24 mg/d, were compared with untreated patients in 2 ways. The ADAS-cog/11 scores of patients treated with galantamine for the first 12 months were compared with those of a clinically and demographically similar historical control group of mild to moderate AD patients who had received placebo for 12 months in an earlier multicenter trial. All placebo-treated subjects of the earlier trial whose baseline ADAS-cog/11 score was within 1 SD of the baseline ADAS-cog/11 score of the present subjects receiving continuous 36-month galantamine therapy comprised the historical control group. There was no significant (\(P = .46\)) difference in baseline ADAS-cog/11 scores between these groups. The 194 galantamine-only–treated subjects in the present study did not differ significantly from the 186 subjects in the historical placebo group by sex (females, 56.7% vs 56.6%; \(P = .88\)) or age (mean ± SD, 76.1 ± 5.9 vs 74.1 ± 5.2 years; \(P = .19\)).

The slope of ADAS-cog/11 scores over time of subjects receiving galantamine, 24 mg/d, continuously for up to 36 months was compared with that of mathematically predicted ADAS-cog/11 scores of untreated subjects.\(^4\) Stern and colleagues\(^4\) determined the quadratic relationship between ADAS-cog/11 scores and the annual rate of cognitive decline in AD patients followed up longitudinally before the introduction of cholinesterase inhibitor treatment. After 3 years, the ADAS-cog/11 scores of untreated patients at a comparable initial level of dementia as that of the actual galantamine-treated subjects at study enrollment were predicted to increase by 20.5 to 22.0 points.\(^4\)

Also, the validity of the predicted slope of ADAS-cog/11 scores over time of untreated patients was estimated by comparing it with the slopes of the 6-month double-blind placebo group in trial 1 and of the 12-month historical placebo group.

An inverted responder analysis was performed for the 119 patients who completed 36 months of continuous galantamine treatment. The percentage of responders was categorized as follows: 0-point or fewer increase, 4-point or fewer increase, 7-point or fewer increase, 10-point or fewer increase, and 20-point or fewer increase on the ADAS-cog/11. This analysis was used to evaluate the number of patients who, after receiving galantamine continuously for 36 months, had better cognitive function than that predicted for untreated patients.

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#### STATISTICAL ANALYSIS

The efficacy analysis was a traditional observed-cases analysis. The baseline visit of the 3- or 6-month double-blind study was used as the baseline examination in this study. Assessment times (time from baseline of the original double-blind studies) were months 12, 18, 24, 30, and 36. The main analysis was based on change from baseline to month 36. Within-group comparisons for the change from baseline or the initial visit were performed using the paired t test.
The demographic and baseline characteristics of all groups are given in Table 1. One hundred ninety-four US patients who had received continuous galantamine therapy from the inception of trials 1 and 2 were enrolled into the multiyear long-term extension study. Of these patients, 119 (61.3%) completed the 36-month study. The most common reasons for discontinuation were AEs and withdrawal of consent. Adverse events occurring in 10% or more of patients treated with galantamine for up to 36 months are listed in Table 2.

SAFETY

Galantamine, 24 mg/d, was well tolerated when administered for 36 months. Most AEs observed were transient, of mild to moderate intensity, and qualitatively similar to those of previous trials. However, the nausea and vomiting observed frequently in short-term trials were uncommon in this study. The AEs seen most frequently were agitation, insomnia, and depression. Few AEs were rated severe. The most common severe AEs were pneumonia (3.7%), falls (3.4%), and injury (3.1%). There were no clinically relevant changes in laboratory values, vital signs, or electrocardiographic readings.

COGNITION

The change from baseline in ADAS-cog/11 scores for patients receiving galantamine for 36 months is illustrated in Figure 1. The ADAS-cog/11 scores at 12 months did not differ from baseline, whereas the ADAS-cog/11 scores of patients in the historical placebo group increased by a mean±SE of 6.26±0.54 points. Patients continuously treated with galantamine, 24 mg/d, did not experience a cognitive decline similar to that in the historical placebo group at 12 months until month 24. Furthermore, the ADAS-cog/11 scores of patients continuously treated with galantamine over 36 months increased by only a mean±SE...
of 10.2±0.9 points vs the 20.5- to 22.0-point increase predicted by the equation of Stern et al. Patients continuously treated with galantamine maintained ADAS-cog/11 scores at or above baseline for the first 12 months, and gained approximately 18 months in preservation of cognition relative to the equation of Stern et al.

The slope of cognitive decline observed during 36 months of continuous galantamine treatment was significantly less steep than that predicted by the equation of Stern et al (P = .03). In contrast, the decline over 6 months of the trial 1 placebo-treated subjects and the decline over 12 months of the historical placebo-treated subjects were almost identical to that predicted by the equation of Stern et al. Assuming that these slope similarities would persist if the placebo groups had been followed up for 36 months, these findings support the validity of the decline predicted by the equation of Stern et al as a comparison for that observed over 36 months of continuous galantamine therapy.

Results of the inverted responder analysis, presented in Figure 2, reveal that 21 (17.6%) of the 119 patients who received continuous therapy with galantamine, 24 mg/d, for 36 months maintained cognitive function at or above baseline (ADAS-cog/11 score unchanged or decreased). More than half of the patients had an increase of 10 or fewer points on the ADAS-cog/11 after 36 months, substantially less than the expected decline in cognitive function (≤20-point increase on the ADAS-cog/11) for untreated AD patients as predicted by the equation of Stern et al.

The positive effects of long-term galantamine treatment could not be attributed to differential rates of decline between those who completed and those who withdrew from the study. The comparison of slopes for the completed and discontinued populations demonstrated that the 181 patients who completed the study were not statistically different (P > .40) from the overall study population, including patients who discontinued therapy for any reason (n = 144) (Figure 3).

These data support the hypothesis that continuous galantamine treatment slows the rate of cognitive decline in AD patients for up to 3 years. On average, patients treated with galantamine, 24 mg/d, maintained cognitive function at pretreatment baseline levels for the first 12 months of therapy. At end point, cognitive decline in galantamine-treated patients was delayed by approximately 18 months vs the predicted decline in untreated AD patients. Almost one fifth of patients had cognitive function at or above prerandomization levels by the end of 36 months of galantamine treatment, and greater than 50% demonstrated improvement in cognition vs that projected for untreated patients. The similarity between the slopes of ADAS-cog/11 score decline in the historical placebo group and as predicted by the equation of Stern et al supports the validity of this mathematical modeling approach for estimating cognitive decline in AD patients. Because untreated AD patients show progressive cognitive decline, maintaining cognitive function at baseline levels or delaying cognitive decline should be viewed as treatment benefits. Together with findings from other studies, these results support the argument for early diagnosis and treatment and support the hypothesis that AChE1 treatment slows AD progression.

Enhancement of cholinergic neurotransmission might slow progression in AD patients by several possible mechanisms. Muscarinic acetylcholine receptor stimulation favors nonamyloidogenic processing of amyloid precursor protein in cell lines and primary neuronal cultures. Muscarinic acetylcholine receptor stimulation also reduces phosphorylation of the cytoskeletal protein tau in pheochromocytoma 12 cells transfected with M1 muscarinic acetylcholine receptors. Allosteric modulation of nicotinic acetylcholine receptors (nAChRs) by galantamine also could slow AD progression. The density of nAChRs decreases in AD patients. Loss of nAChRs is strongly correlated with AD severity. Stimulation of nAChRs inhibits the neurotoxic effects of β-amyloid in cultured neurons; this effect
is mediated by the α2β, nAChR widely present in the cerebral cortex, and improves learning, memory, and attention.

Furthermore, autoradiographic, histochemical, and brain imaging studies in AD patients indicate that nAChR loss is more severe than loss of muscarinic acetylcholine receptors or choline acetyltransferase. Galantamine's ability to modulate nAChRs, and inhibit acetylcholinesterase, may contribute to its broad spectrum of therapeutic benefits and sustained effectiveness in AD patients.35

Galantamine seemed effective and was safe and well tolerated in AD patients with mild to moderate dementia for 36 months. Although these results suggest long-term positive effects on clinical decline in AD patients treated with galantamine, conclusions are limited by the lack of biological indicators of disease progression and the absence of a true long-term placebo control group. Even more convincing demonstrations of disease-modifying effects of AChEIs hopefully will emerge from ongoing placebo-controlled trials in persons with mild cognitive impairment.

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