ABSTRACT

Galantamine is a new treatment for Alzheimer’s disease (AD) with a dual-action mechanism to enhance cholinergic function: inhibition of acetylcholinesterase and modulation of nicotinic acetylcholine receptors. This article summarizes the interim results of an 18-month extension to a published 6-month, randomized, placebo-controlled trial of galantamine (24 mg/day and 32 mg/day). The results show that the cognitive benefits with galantamine continue for at least 24 months. Those patients switching from placebo to galantamine (24 mg/day) regained some cognitive benefit but did not attain the benefits of those patients randomized to drug. Patients who were taking 24 mg/day throughout the entire study maintained activities of daily living for 12 months; activities somewhat decreased in patients who began with 32 mg/day and switched to 24 mg/day; activities were not restored in patients who spent 6 months on the placebo before switching to galantamine 24 mg/day.

Galantamine is one of the newer acetylcholinesterase (AChE) inhibitors used to treat the loss of cholinergic neurons in the brain’s hippocampus and cortex, which clinicians believe is the cause of cognitive decline in patients with Alzheimer’s disease (AD). Galantamine has a dual-action mechanism to enhance acetylcholine function: competitively and reversibly inhibiting AChE and potentiating cholinergic nicotinic neurotransmission by allosterically modulating nicotinic acetylcholine receptors. Although it is not clear if these mechanisms can explain the benefits of galantamine observed in patients with AD, it does provide a rationale for further exploration.

STUDY DESIGN

The study reported here is an open-label extension of a previously published study of galantamine in 636 patients with mild to moderate probable AD, according to the National Institute of Neurological Disorders and Stroke and the Alzheimer Disease and Related Disorders Association criteria. The patients had Mini-Mental State Examination (MMSE) scores ranging from 11 to 24, enriched AD Assessment Scale, cognitive subscale (ADAS-cog/11) scores of at least 12, and no evidence of metabolic or endocrine disturbances. The patients had been randomized to 1 of 3 treatment groups: placebo, galantamine 24 mg/day, or galantamine 32 mg/day. Dose escalations from 8 mg/day to 24 or 32 mg/day were made at 2-week intervals. Maintenance dosing continued for the remaining 5.5 months, after which all patients could participate in an open-label phase of the study taking galantamine 24 mg/day.
mg/day. All patients originally in the double-blind study and then switched to the open-label phase were titrated up to 24 mg/day over 3 weeks. There were no significant differences in age, gender, medical condition, duration of cognitive deficits, MMSE score, ADAS-cog score, or Disability Assessment for Dementia (DAD) scale score among the treatment groups.

Patients receiving at least 24 mg/day of galantamine maintained baseline ADAS-cog/11 and DAD scores (cognitive and daily function) throughout the first 12 months of the study, and their cognitive and global function improved after only 6 months.

This study reports on an open-label extension to the original 6-month double-blind study. For ethical reasons, the placebo-controlled phase could not continue into the open-label period because of the beneficial results reported after 6 months of galantamine treatment. So, the open-label data are compared to a historical placebo group from a previous study of sabeluzole (N = 261) which continued for 1 year and extrapolated data thereafter. Overall, the demographics of the historical placebo group at baseline are very similar to those of the galantamine group; however, the galantamine group had slightly lower MMSE and DAD scores and had slightly better ADAS-cog/11 scores.

RESULTS

The outcome measures for this study were the change from baseline ADAS-cog/11 and DAD scores, as in the double-blind study. Patients who had initially been taking placebo and switched to galantamine 24 mg/day gained some benefit on the ADAS-cog/11. The benefit, however, was never to the extent of those patients who originally received galantamine 24 mg/day or 32 mg/day in the double-blind study and 24 mg/day throughout the open-label phase. For the DAD score, which reflects activities of daily living, patients who had been receiving galantamine 24 mg/day throughout the study had DAD scores that were not significantly different from baseline at 1 year. Patients who originally received galantamine 32 mg/day and switched to 24 mg/day in the open-label phase lost some of their initial benefit from the higher dose. Patients who were originally in the placebo group and then switched to galantamine 24 mg/day did not attain the benefits gained by the 24 mg/day group, suggesting that once patients lose the ability to perform activities of daily living, they may never regain that ability.

The historical placebo group was used to compare galantamine-treated patients to placebo patients at 1 year and at 2 years postbaseline. Because placebo data were only available for 12 months, 2 methods were used to extrapolate further decline after 12 months: linear extrapolation for ADAS-cog/11 (change from baseline) data or extrapolation based upon the rate of decline in the most recent 6 months. Those who had been taking galantamine (24 mg/day or 32 mg/day) throughout the double-blind and open-label phases had a decline in ADAS-cog/11 score of 5.4 ± 1.1 points at 24 months as compared with 12.5 ± 17.3 and 14.2 ± 17.3 in the extrapolated placebo group.

Patients maintained good tolerability for galantamine throughout the open-label phase, as originally reported in the Raskind et al study. The most common adverse events were anorexia and weight loss, which decreased over time.

CONCLUSIONS

Patients treated with galantamine continue to maintain cognition and daily function after 24 months of treatment and to maintain function for at least 12 months. Patients receiving placebo initially were able to regain some cognitive benefit when they switched to galantamine 24 mg/day, but they did not attain the same benefits as patients who were continuously on the drug. Galantamine is safe and well tolerated. —MGG

REFERENCES