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Galantamine treatment in Alzheimer's disease with cerebrovascular disease: responder analyses from a randomized, controlled trial (GAL-INT-6)

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Abstract

Alzheimer's disease combined with cerebrovascular disease (AD with CVD) is associated with progressive decline, with CVD impacting AD onset and severity of progression. Subjects with confirmed diagnosis of AD with CVD were treated with galantamine during a six-month, randomized, placebo-controlled trial ($N = 285$). Responder analyses were performed for cognitive, behavioural and functional outcome measures. Galantamine treatment resulted in significantly greater cognitive and functional improvements compared with placebo at six months, and a significantly higher percentage of treatment responders. The proportion of responders demonstrating improved or maintained cognition on the 11-item AD assessment scale-cognitive subscale (ADAS-cog/11) was 60.5% for galantamine versus 46.0% for placebo ($P = 0.013$). The proportion of patients responding by at least four-points on the ADAS-cog/11 was significantly greater for the galantamine group compared with placebo (33.6% versus 17.2%; $P = 0.003$). Seventy-five percent of galantamine-treated subjects improved or remained stable as assessed by CIBIC-plus compared with 53.6% on placebo ($P = 0.0006$). Significantly higher responder rates were observed with galantamine for behaviour (64.9% versus 56.6%; $P = 0.024$), and numerically favourable responder rates were seen with galantamine for activities of daily living. Treatment-emergent adverse events were generally related with the gastrointestinal system (nausea 20% versus 10%; vomiting 12% versus 5%; galantamine and placebo groups, respectively). Three deaths occurred during double-blind treatment: 2 of 188 subjects receiving galantamine, and 1 of 97 subjects receiving placebo. These findings are consistent with a broad range of cognitive, functional and behavioural benefits with galantamine across the spectrum of AD and AD with CVD.

Keywords

Alzheimer disease, dementia, cerebrovascular accident, cardiovascular diseases, vascular dementias, galantamine

Introduction

There is growing evidence that Alzheimer's disease (AD) frequently co-exists with significant cerebrovascular (CVD) pathology (Jellinger, 2002; Jellinger and Attems, 2006; Jellinger, 2007). Clinically, this overlap is AD with cerebrovascular disease (AD with CVD). The term 'mixed dementia' is sometimes used to describe this condition, but is also used to describe vascular dementia with both cortical and subcortical features so AD + CVD is more precise. Clinical differentiation of AD from AD with stroke history or vascular risk factors is complicated by symptom overlap (Lopez *et al.*, 2005; Jellinger, 2007). A diagnosis of AD does not preclude the presence of CVD, and dual diagnosis is important. Relative with AD alone, AD with CVD may involve a more

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unpredictable cognitive decline. AD with CVD patients are at a greater risk of morbidity and mortality, as they have additional vascular risk factors, with CVD impacting the presence and severity of clinical symptoms of AD (Snowdon *et al.*, 1997; Pasquier *et al.*, 1998; Rieske *et al.*, 2004; Fitzpatrick *et al.*, 2005). The recognition that AD and CVD commonly coexist and interact, requires an inclusive clinical perspective that considers the impact of both AD and cerebrovascular pathology on cognitive decline.

A testable hypothesis is whether the co-existence of AD and CVD results in a clinical syndrome that may be amenable to therapeutic approaches on the basis of AD pathophysiology. Degeneration of cholinergic neurotransmission appears to underlie the dementia syndrome in both AD and AD with CVD (Erkinjuntti, 2001). Cerebrovascular lesions, such as diffuse white matter lesions are frequently located in subcortical brain regions that disrupt basal forebrain-cortical pathways (Swartz *et al.*, 2002; Mesulam *et al.*, 2003). Forebrain cholinergic pathways are required for cognitive processing, and nicotinic acetylcholine receptors are involved in mechanisms of attention (Howe and Price, 2001; Bourin *et al.*, 2003). Cholinergic dysfunction in clinical dementia includes reduction of choline acetyltransferase; the enzyme responsible for biosynthesis of acetylcholine, death of forebrain cholinergic neurons and decreases in nicotinic receptor expression (Grantham and Geerts, 2002).

Galantamine is a reversible, competitive acetylcholinesterase inhibitor that is also postulated to modulate multiple subtypes of nicotinic acetylcholine receptors (Samochocki *et al*., 2003). These two complementary mechanisms are unique among medications currently used to treat AD. The precise physiological links that translate these pharmacological actions to cognitive and functional benefits are unknown. Galantamine has shown both short and longer-term benefits in patients with mild-to-moderate AD. Patients treated with galantamine demonstrate improvements compared with placebo across multiple measures of efficacy including: cognition, behaviour and activities of daily living (Raskind *et al.*, 2000; Tariot *et al.*, 2000; Wilcock *et al.*, 2000; Rockwood *et al.*, 2001; Lyketsos *et al*., 2004; Brodaty *et al.*, 2005). Galantamine is the only cognitive enhancer evaluated specifically in AD with CVD in a multicentre, randomized, controlled study that used differential diagnostic criteria from probable vascular dementia (Erkinjuntti *et al.*, 2002, 2003).

Here, we report results of responder analyses of AD with CVD subjects treated with galantamine compared with placebo as secondary analyses of a six-month, randomized-controlled trial (Pasquier *et al.*, 1998). Responder analyses facilitate interpretation of treatment effects in clinical trials for practicing clinicians, and are now required by European regulatory authorities for many therapeutic areas, including AD (Winblad *et al.*, 2001; Kieser *et al.*, 2004). Responder analyses provide clinically meaningful assessments of subjects exhibiting therapeutic benefits for active treatment versus control conditions.

An operational definition of treatment responders in AD includes the proportion of patients that experience a prespecified degree of improvement in cognition and/or an improvement, or stabilization in functional and global abilities. With this approach as the analytical framework, the aims of the present study were: 1) to evaluate the proportion of therapeutic responders on galantamine versus placebo for important indicators of cognitive function, behaviour and activities of daily living, 2) to evaluate the incidence of adverse events for AD with CVD patients when treated with galantamine as a measure of risk benefit and 3) to discuss the importance of treating patients within the clinical spectrum of dementia because of the impact of CVD on the clinical progression of AD.

Materials and methods

Responder analyses were specified in an overall analysis protocol of a randomized, placebo-controlled trial of galantamine treatment of AD with CVD, and probable vascular dementia (Erkinjuntti *et al.*, 2002, 2003).

Responder analyses were conducted to evaluate treatment effects across cognitive, behavioural and functional endpoints. Detailed clinical trial methods and safety evaluations are published (Erkinjuntti *et al.*, 2002, 2003) and are summarized briefly below.

Study population

Male or female outpatients with AD plus CVD were confirmed according to the National Institute of Neurological and Communicative Disorders and Stroke and AD and Related Disorders Association (NINCDS–ADRDA) criteria (McKhann *et al.*, 1984), together with neuroimaging evidence of CVD (assessed at local centres) within 12 months. Evidence of CVD on a recent scan (within 12 months) included multiple large-vessel infarcts or a single, strategically placed infarct (angular gyrus, thalamus, basal forebrain, territory of the posterior or anterior cerebral artery) or at least two basal ganglia and white-matter lacunae or white-matter changes involving at least 25% of the total white matter. Documentation of focal neurological signs consistent with previous stroke and of CVD was required.

Inclusion criteria specified subjects had dementia onset between 40 and 90 years of age, mini-mental state examination (MMSE, Folstein *et al.*, 1975) score of between 10 and 25, AD assessment scale cognitive subscale (ADAS-cog; Rosen *et al.*, 1984) score of 12 or greater and a care provider who was a reliable informant.

Patients were excluded from the study if they had evidence of neurodegenerative disorders other than AD, cognitive impairment because of other causes, cardiovascular disease thought likely to prevent completion of the study, epilepsy, clinically significant psychiatric illness, history of significant substance abuse, hepatic, renal, pulmonary, metabolic or endocrine disturbances, active peptic ulcer or had received an investigational medication within 30 days prior to screening. Any medications prescribed for the treatment of dementia, or with anti-cholinergic or cholinomemetic properties were discontinued prior to study entry.

Study design

Patients meeting the diagnostic criteria for AD with CVD were evaluated as a subpopulation of a larger, randomized, double-blind,

placebo-controlled, multicentre trial of galantamine (24 mg/day) versus placebo on measures of cognition, behaviour and activities of daily living in subjects with AD with CVD or vascular dementia (Erkinjuntti *et al.*, 2002).

Briefly, the study consisted of a four-week single-blind placebo run-in period followed by randomization to galantamine 24 mg/day or matching placebo administered twice daily. Patients were initiated on galantamine 4 mg/day within the first week, with weekly dose escalation of 4 mg/day until 24 mg/day was reached in week 6. The randomization ratio was 2:1 for galantamine versus placebo to minimize exposure to placebo.

Efficacy assessments

Prespecified primary efficacy assessments in the original trial relied on observed-case analyses at six months. Measures included the 11-item AD assessment scale-cognitive subscale (ADAS-cog/11, Rosen *et al.*, 1984) to evaluate cognitive ability, and the clinician's interview-based impression of change plus caregiver input (CIBIC-plus, Schneider *et al.*, 1997). The CIBIC-plus scale provides an assessment of a patient's condition independent of other assessment scales. ADAS-cog/11 data were collected at screening, baseline, week 6, month 3 and month 6. To reduce variability due to circadian fluctuations in cognitive status, the ADAS was to be completed at the same time of day, preferably before noon. The CIBIC-plus was completed at baseline, month 3 and month 6, as were the neuropsychiatric inventory (NPI, Cummings, 1997) and disability assessment in dementia scale (DAD, Gelinas *et al.*, 1999) Informant interview contributed information to CIBIC-plus, NPI and DAD assessments. The NPI assesses the frequency and severity of symptoms across 10 behavioural domains, although the DAD scores the capacity to execute daily activities across six domains described as: basic, initiation, instrumental, leisure, performance and planning. Mean changes from baseline over time were calculated, and tests for significance were conducted using a mixed-effects model incorporating: treatment, country and time as factors.

Responder analyses

Treatment responders on ADAS-cog/11 were defined as those subjects who maintained or improved cognitive function. The ADAS-cog/11 ranges from 0 to 70 with reductions in score indicating improved cognitive function. The proportion of patients who remained stable, improved by at least 4 points and those that improved by at least 7 points were computed for the galantamine-treated and placebo groups, respectively. Responder groups were thus categorically defined as three analytic groups that exhibited: 1) a greater than or equal to 0 point change, that is cognitive function improved or remained stable over time, 2) a greater than or equal to 4-point improvement or 3) greater than or equal to seven-point improvement in ADAS-cog/11 scores. Responders on CIBIC-plus scale were identified as those placebo or galantamine-treated subjects who improved or remained stable, that is, a score of $\leq$4-points. Possible treatment effects on behaviour and responder subgroups were assessed using the total score of the NPI. Impact of treatment on activities of daily living was evaluated using total DAD score and subitems with $\geq$0-point change marking improvement. As secondary analyses, the study was not powered to detect significance at the level of individual subitems of the assessment scales although magnitude and direction of change on subitem scores were evaluated for trends. The Cochran-Mantel–Haenszel (CMH) test, controlling for baseline and country was used to evaluate possible treatment effects. For change in NPI scores, CMH analyses of between group differences were also controlled for anti-psychotic medication use. As stated above, interpretation of the results focused on data trends with an hypothesis-generating intent and as such no adjustments were made for multiple testing (see comments on this approach by Perneger, 1999). Descriptive statistics were used to assess and report frequency of adverse events. Data were analysed using Microsoft Excel and SAS® software platforms.

Results

Demographics and patient characteristics

A total of 285 subjects (188 galantamine, 97 placebo; Figure 1) with a confirmed diagnosis of AD with CVD were included in this study.

A higher proportion of galantamine-treated subjects than placebo subjects discontinued the trial, mostly because of adverse events (13.3% versus 5.2%). Other reasons for discontinuation were: death (1.1% versus 1.0%), lack of efficacy (0 versus 0.5%), loss to follow-up (1.0% versus 0), non-compliance (1.0% versus

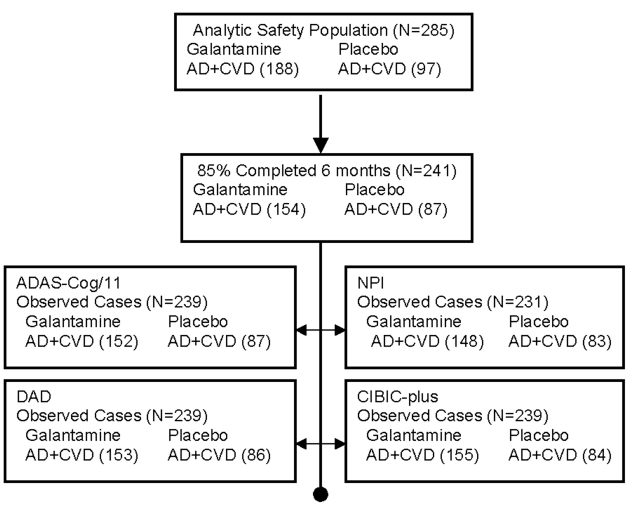

Figure 1 AD with CVD safety population and available observed case data for responder analyses. Analytic Ns (%) across all cognitive and functional outcomes are unequal because subjects may have 1 or more incomplete assessment during the month 6-study visit as verified on individual case report forms. For example, ADAS-cog/11 subject data were included only if all 11 assessments were completed. Ns provided here served as denominators for the responder analyses reported in the results section.

1.1%), consent withdrawn (1.0% versus 1.1%) and other (1.0% versus 1.1%) for galantamine and placebo groups, respectively. Overall, 85% of subjects completed six months of double-blind treatment and these subjects were included in the completer population for responder analyses ($N = 154$ galantamine 24 mg/day, $N = 87$ placebo, see Figure 1). Subject treatment assignment and demographic characteristics are provided for the safety population in Table 1. Age, gender, race, age of onset of cognitive problems and baseline cognitive and functional assessment scores were comparable for the galantamine-treated and placebo groups. Mean age (±SD) for AD with CVD patients was 75.8 ± 6.8 years and 77.6 ± 5.9 years for the galantamine and placebo groups, respectively. Currently active, concomitant cardiovascular disease was reported for 66% of the galantamine-treated group and 70% for the placebo group

Table 1 Baseline characteristics of AD with CVD patients who received galantamine or placebo during six-month double-blind treatment (safety population)

	Galantamine $N = 188$	Placebo $N = 97$
Age	75.8 ± 6.8	77.6 ± 5.9
Female, %	53	51
Race, % white	100	99
Weight, kg	69.3 ± 12.9	67.1 ± 13.4
Age at onset of cognitive problems	72.8 ± 7.3	75.2 ± 6.0
Subjects, % with cardiovascular disease at baseline	66	70
Cognitive function		
Sum of MMSE[a]	20.5 ± 4.0	20.0 ± 3.6
ADAS-cog/11[b]	22.7 ± 9.1	24.8 ± 10.4
DAD[c]	69.5 ± 23.1	65.6 ± 23.6
NPI[d]	11.0 ± 11.6	11.4 ± 11.8

Baseline characteristics for entire trial population are published (Erkinjuntti, 2002). Twenty-four months after database lock, discrepancies in dementia type between clinical source documents and the database were detected for three patients. Although these discrepancies exist, they did not affect efficacy or safety conclusions. All data reported here are from the locked six-month double-blind efficacy and safety database.

[a]MMSE baseline scores were available for $N = 188$ galantamine, $N = 97$ placebo. Scale ranges from 0 5 not testable to 30 5 no cognitive impairment, with a score ⩽23 indicating cognitive impairment.

[b]ADAS cog-11 baseline scores were available for $N = 182$ galantamine, $N = 96$ placebo. Scale ranges from 0 to 70 with lower scores indicating better cognitive function.

[c]DAD baseline scores were available for $N = 183$ galantamine, $N = 96$ placebo. Scale ranges from 0 to 100 with higher scores indicating greater ability to perform activities of daily living.

[d]NPI baseline scores in AD with CVD group were available for $N = 179$ galantamine, $N = 94$ placebo. Scale ranges from 0 to 120 with lower scores indicating less impairment.

Baseline values are reported as mean ± SD unless otherwise indicated.

Cognition, functional ability and behaviour

Mean change from baseline in ADAS-cog/11, total DAD and NPI scores for AD with CVD patients are shown in Figure 2 and are consistent with previously published endpoint and completer results from the entire study population (Erkinjuntti *et al.*, 2002).

At six months, the subgroup of AD with CVD patients treated with galantamine exhibited improved cognitive abilities (Figure 2a; $P < 0.001$). CIBIC-plus results for AD with CVD patients were significantly better in the galantamine-treated group ($P < 0.001$; see Table 2), and the mean change in total DAD was positive for galantamine-treated patients versus placebo (Figure 2b; $P = 0.003$). Mean change from baseline in total NPI score at six months reflected numeric improvement for the galantamine group, although this difference did not reach statistical significance ($P = 0.120$). Treatment responders were defined as the number and proportion of AD with CVD patients who maintained or exhibited improvement in cognitive function, behaviour, or activities of daily living on the basis of prespecified criteria described in the above methods section for observed case analyses at six months.

The proportion of patients whose ADAS-cog/11 scores improved by at least 0, 4 or 7 (decrease in total scores versus baseline) was defined as responder (0), responder (4), responder (7) subgroups, respectively (see Table 2). The responder rates for ADAS-cog/11 according to all three definitions were significantly better for galantamine versus placebo ($P = 0.013$, $P = 0.003$, $P = 0.006$, respectively). At month 6, the proportion of responders in the galantamine group who improved or exhibited no deterioration in ADAS-cog/11 score was 60.5% and significantly greater than that observed for the placebo group (46%; Table 2; $P = 0.013$; Figure 3). The proportion of responders who improved by 4-points or more on ADAS-cog/11 was 33.6% galantamine versus 17.2% placebo ($P = 0.003$). The proportion of subjects who improved by 7-points or more (which clinically is considered an exceptional response), was 16.5% galantamine versus 5.8% placebo ($P = 0.006$). Although these values represent a relatively small proportion of patients, it is worth noting that over two times the frequency of galantamine-treated subjects versus placebo-treated subjects exhibited a greater than average treatment response (i.e., ⩾7-point ADAS-cog improvement). Responder analyses of total DAD, NPI and CIBIC-plus data are also summarized in Table 2 and illustrated for AD with CVD patients in Figure 3.

Seventy-five percent of AD with CVD patients were positive responders with galantamine treatment as assessed by CIBIC-plus at month 6. The proportion of DAD treatment responders at month 6 was 51%, and numerically better than the placebo group (39.5%) but this difference did not reach statistical significance ($P = 0.105$). The evaluation of mean change in DAD scores over time for AD with CVD patients, however, showed significant separation between treatment groups (Figure 2b, $P = 0.003$). The treatment difference in total DAD score over time is clinically meaningful. Further exploratory analyses of individual DAD items, revealed that four of six subitems (*basic:* 71.9% responders on

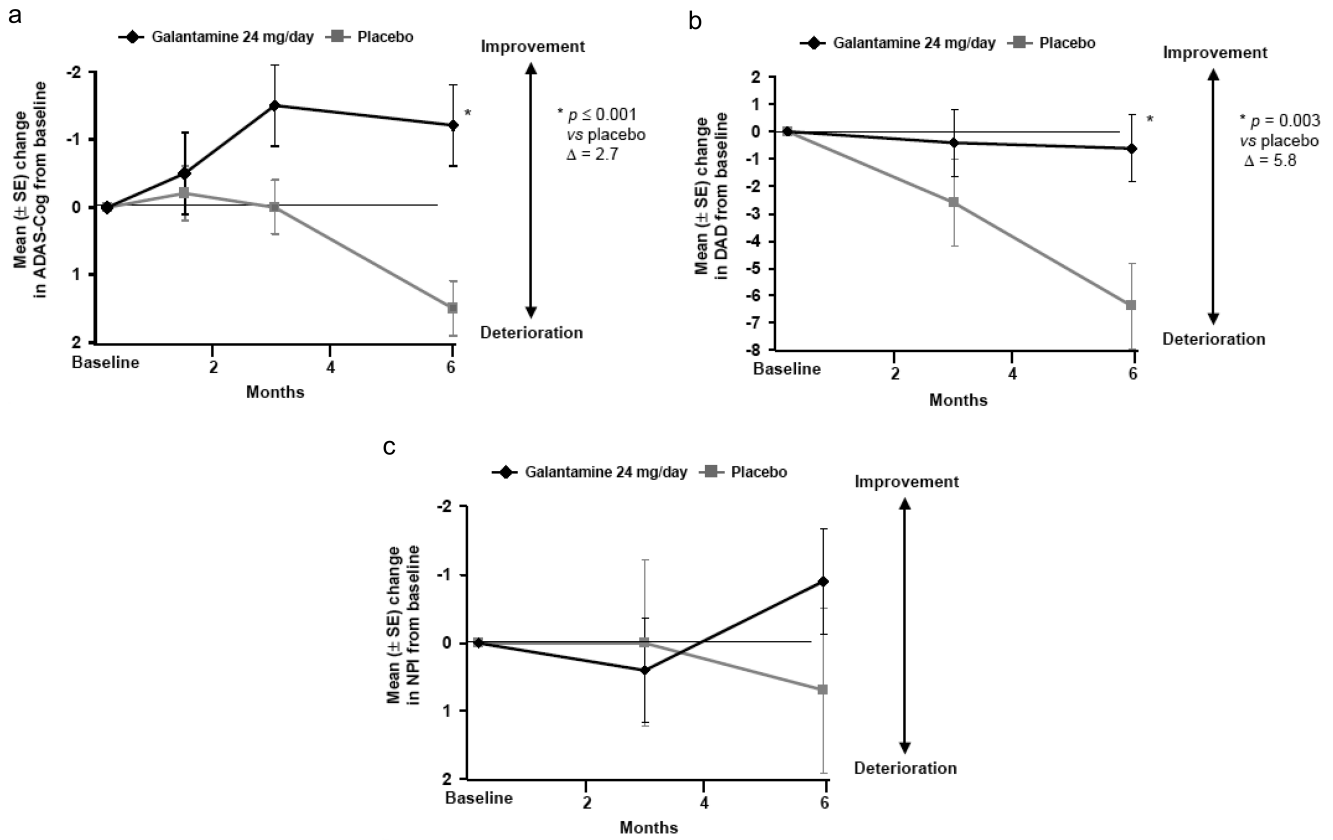

Figure 2 a) Mean change from baseline in ADAS-cog/11 ($P < 0.001$ versus placebo). Magnitude of response at month 6 is 2.7. b) Mean change from baseline in total DAD score ($P = 0.003$ versus placebo). Magnitude of response is 5.8. c) Mean change from baseline in total NPI score ($P = 0.120$), with overlapping standard errors at month 6. Observed case analyses and all values are mean ± SE.

Table 2 Responder analyses

	GAL % (*N*)	PLA % (*N*)	*P*-value
ADAS COG/11			
Responder (0)	60.5 (92)	46.0 (40)	*$P = 0.013$
Responder (4)	33.6 (51)	17.2 (15)	*$P = 0.003$
Responder (7)	16.5 (25)	5.8 (5)	*$P = 0.006$
CIBIC-plus			
Stable, improved	74.8 (116)	53.6 (45)	*$P = 0.0006$
DAD total score			
≥0-point increasing	51.0 (78)	39.5 (34)	$P = 0.105$
NPI total score			
≥0-point decreasing	64.9 (96)	56.6 (47)	*$P = 0.024$

*Significant differences between galantamine and placebo treatment groups. Responder categories reflect improvement in scores from baseline and are based on observed case analyses, with denominators provided in patient flow in Figure 1.

galantamine versus 54.7% placebo, $P = 0.036$; *initiation:* 63.4% versus 48.8% placebo, $P = 0.031$; *instrumental:* 56.6% versus 44.2% placebo, $P = 0.024$; *leisure:* 80.4% versus 66.7% placebo, $P = 0.038$) exhibited significantly higher responder rates for galantamine treatment than placebo, whereas performance (54.0% galantamine versus 43.0% placebo, $P = 0.078$) and planning (58.2% galantamine versus 45.4%, $P = 0.057$) trended in favour for the galantamine group. As described in the methods, these subitem analyses were completed with an hypothesis-generating intent focusing on directional trends in the data only.

A mean decrease in total NPI score was detected in galantamine-treated patients at six months, with a small increase for the placebo group. This was a numerical trend for improvement with galantamine, although it did not reach statistical significance at month 6 (Figure 2c). The proportion of galantamine-treated responders for behavioural effects was significantly greater than for the placebo group as measured by NPI (GAL 64.9% versus PLA 56.6%; $P = 0.02$; Table 2, Figure 3).

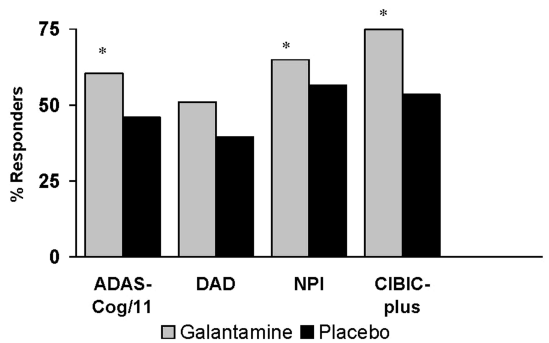

Figure 3 Proportion of positive responders as assessed by ADAS-cog/11 (*$P = 0.013$), DAD ($P = 0.105$), NPI (*$P = 0.024$), CIBIC-plus by treatment group (*$P = 0.0006$) for galantamine versus placebo, respectively. No adjustments were made for multiple testing.

Safety and tolerability

Galantamine was generally well-tolerated in this AD with CVD patient population, but higher proportions of patients (Table 3) treated with galantamine versus placebo experienced nausea (20% versus 10%), vomiting (12% versus 5%), or dizziness (12% versus 7%). Most adverse events were mild-to-moderate in severity and of short duration. Treatment-emergent nausea and/or vomiting were not unexpected with galantamine treatment given its cholinergic properties, and a weekly dose escalation schedule specified by the study protocol during the titration phase of the trial. Currently, a more gradual dose escalation of galantamine is recommended; typically after a minimum of four weeks upon initiating treatment. Overall, the tolerability profile of galantamine for AD with CVD patients was similar to that observed previously in pivotal trials for galantamine in patients with AD alone. (Table 3).

Cardiovascular events (≥2%) reported during the trial included: hypertension (4% versus 0%), arrhythmia (3% versus 0%), ECG abnormal (0% versus 2%), hypertension aggravated (0% versus 2%) for galantamine-treated subjects and the placebo group, respectively. Cerebrovascular disorder(s) were reported for 4% of placebo-treated subjects and 3% for galantamine. Three deaths were reported in the AD with CVD population during double-blind treatment: 2 of 188 subjects receiving galantamine, and 1 of 97 subjects receiving placebo. Serious adverse events reported with deaths included ventricular fibrillation, respiratory disorder and coronary artery disorder. According to the trial investigators, the deaths were of doubtful or no relationship to study treatment. No imbalance in mortality was observed during six months of double-blind galantamine treatment in this AD with CVD study population. These findings were not unexpected, and are perhaps, lower than natural history would predict in an elderly patient population with known, currently active cardiac disease and vascular risk factors.

Table 3 Adverse events occurring in at least 5% of patients with AD with CVD[a] ($N = 285$), with qualitative comparison to adverse events in patients treated with 16 or 24 mg/day for mild-to-moderate AD only (pooled data from four placebo–controlled trials ($N = 1841$))[b]

Adverse event	AD + CVD Gal 24 mg/day ($N = 188$)	AD + CVD Placebo ($N = 97$)	AD GAL 16, 24 mg/day ($N = 1040$)	AD Placebo ($N = 801$)
Nausea	20%	10%	24%	9%
Vomiting	12%	5%	13%	4%
Dizziness	12%	7%	9%	6%
Abdominal pain	7%	8%	5%	4%
Diarrhoea	7%	6%	9%	7%
Depression	6%	7%	7%	5%
Headache	6%	7%	8%	5%
Fatigue	5%	6%	5%	3%
Upper respiratory infection	5%	4%	3%	4%

[a]Adverse events in ≥5% of subjects, and with a reporting frequency greater with galantamine treatment than with placebo.

[b]The most common adverse events listed in galantamine product label from four placebo-controlled trials in mild-to-moderate AD (Ortho McNeil, 2006).

Discussion

AD with CVD results in clinical symptoms that respond to galantamine treatment. The aim of this study was to explore the possible therapeutic benefits of galantamine in AD with CVD using responder rate methodology. With the significant cost of large-scale, prospective studies, the utilization of existing clinical trial databases such as the analyses presented here, remain a rich source of valuable information for clinicians and their patients. Responder rates provide clinically meaningful data that enable estimates and proportional comparisons of patients who may benefit from treatment (Keiser *et al.*, 2004). Each patient contributes data relative to his or her own pretreatment baseline. Current responder definitions to anti-dementia treatment emerge from the design of clinical trials used to obtain regulatory approvals using several cognitive, functional and behavioural endpoints. One definition commonly used in such studies is a four-point (or more) improvement relative with baseline on ADAS-cog/11 over six months (Winblad *et al.*, 2001). Applying this responder definition to the ADAS-cog/11 results provided here, twice as many galantamine-treated subjects were positive responders as compared with placebo (33.6% of AD with CVD patients on galantamine were positive responders compared with 17.2% on placebo, $P = 0.003$). These results are consistent with favourable outcomes in the entire trial population that were previously published and based on both observed cases and last observation carried forward (LOCF) methods (Erkinjuntti *et al.*, 2002).

Responder analyses involving functional and behavioural outcomes also showed beneficial treatment effects of galantamine in

AD with CVD patients. AD with CVD patients treated with galantamine showed significantly higher responder rates in global function, behaviour and 4 of 6 items related with activities of daily living. Such benefits with galantamine treatment are important not only for AD with CVD patients, but may have positive implications on the burden of family members, care providers and healthcare resources. The positive outcomes on CIBIC-plus at six months reported previously (Erkinjuntti *et al.*, 2002) support this hypothesis. Future studies are needed to address whether positive responder rates in cognition, function and behavioural outcomes correlate to improved quality of life and reduced caregiver burden for AD with CVD patients.

This study used pragmatic diagnostic/inclusion criteria to reflect real-life practice. One limitation of the design was that neuroimaging was performed (and assessed) locally. This may have reduced the consistency of assessing CVD but, once again, reflects normal clinical practice.

Galantamine was generally well-tolerated in AD with CVD patients, although some gastrointestinal side effects were observed. Eighty-two percent of galantamine-treated patients completed six months of double-blind treatment compared with 89.7% in the placebo group. Reasons for discontinuation included adverse events, loss to follow-up, noncompliance and withdrawn consent. No subjects in the galantamine group discontinued because of lack of efficacy. Consistent with previous clinical experience with galantamine in mild-to-moderate AD (Raskind *et al.*, 2000; Tariot *et al.*, 2000; Wilcock *et al.*, 2000; Rockwood *et al.*, 2001; Brodaty *et al.*, 2005), common treatment-emergent adverse events were generally associated with the gastrointestinal system, with higher rates of nausea and vomiting among patients treated with galantamine versus placebo (Table 3). In this study, patients started on galantamine 4 mg/day in the first week and were then titrated with weekly increments of 4 mg/day until they reached 24 mg/day in week 6. This titration schedule differs from the currently approved galantamine product label for mild-to-moderate AD in which the recommended starting dose is 8 mg/day with dosage increases recommended after a minimum of four weeks (Ortho McNeil, 2006). Qualitative comparisons of adverse event rates from this study with other controlled-clinical trials conducted with galantamine in AD alone, suggest a consistent tolerability profile for AD patients with or without coexisting CVD (see Table 3).

The cognitive and functional improvements with galantamine in AD with CVD patients are of a similar magnitude to those previously reported for galantamine treatment in AD alone (Raskind *et al.*, 2000; Tariot *et al.*, 2000; Wilcock *et al.*, 2000; Rockwood *et al.*, 2001; Brodaty *et al.*, 2005). For AD patients, symptom stability or improvement of 4-points or more on ADAS-cog may represent a 4–12 month delay in disease progression (Cummings, 2003; Feldman *et al.*, 2005). Patients and their response to treatment are, of course, highly variable and will be impacted by many factors including dementia severity at the time of treatment initiation (Doraiswamy *et al.*, 2001). Galantamine has shown long-term benefits (up to one year) in AD with CVD patients (Erkinjuntti, 2003) with improvements in cognition and global measures, and in particular with activities of daily living. These observations support the hypothesis that galantamine treatment in AD patients is not compromized by concomitant CVD – AD with coexisting CVD is still AD. Outcomes for AD with CVD patients appear to be as good as, or better than in AD-alone. Together with the overall safety and low morbidity and mortality observed in this study, these results support a positive benefit:risk profile of galantamine treatment for patients with AD with CVD.

Overall, the positive responder rates with galantamine are consistent with a broad range of cognitive, functional and behavioural benefits reported for patients across the spectrum of AD with CVD, as well as mild-to-moderate AD. Coexisting AD with CVD should not deter from a therapeutic strategy involving cholinergic modulation to limit progression of cognitive decline. Further advances in clinical care of AD with CVD patients will require future studies to characterize modifiable risk factors, together with available symptomatic treatments to ensure meaningful outcomes for patients and their families.

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