

A multinational, randomised, 12-week study comparing the effects of donepezil and galantamine in patients with mild to moderate Alzheimer's disease

Roy W. Jones^{1*}, Hilka Soininen², Klaus Hager³, Dag Aarsland⁴, Peter Passmore⁵, The DONGAL Study Group, Anita Murthy⁶, Richard Zhang⁷ and Ranbir Bahra⁷

¹Research Institute for the Care of the Elderly, St Martin's Hospital, Bath, UK

²Department of Neurology, Kuopio University Hospital, Finland

³Department of Medical Rehabilitation and Geriatrics Henriettenstiftung, Hannover, Germany

⁴Rogaland Psykiatriske Sykehus, Stavanger, Norway

⁵Department of Geriatric Medicine, Queen's University, Belfast, UK

⁶Eisai Inc., Teaneck, New Jersey, USA

⁷Pfizer Inc., New York, USA

SUMMARY

Objectives To compare directly, in the same patient cohort, the ease of use and tolerability of donepezil and galantamine in the treatment of Alzheimer's disease (AD), and investigate the effects of both treatments on cognition and activities of daily living (ADL).

Methods Patients with mild to moderate AD from 14 European centres were randomised to receive open-label donepezil (up to 10 mg once daily) or galantamine (up to 12 mg twice daily) for 12 weeks, according to the approved product labelling. Physicians and caregivers completed questionnaires rating satisfaction with treatment/ease of use in daily practice. Secondary assessments were the ADAS-cog, the MMSE, and the DAD scale to assess ADL. Tolerability was evaluated by reporting adverse events (AEs).

Results Both physicians and caregivers reported significantly greater overall satisfaction/ease of use for donepezil ($n = 64$) compared with galantamine ($n = 56$) at weeks 4, 12, and endpoint (week 12 LOCF; all p -values < 0.05). Significantly greater improvements in cognition were also observed for donepezil versus galantamine on the ADAS-cog at Week 12 and endpoint (p -values < 0.05). ADL improved significantly in the donepezil group compared with the galantamine group at weeks 4, 12, and endpoint (p -values < 0.05). Most AEs were mild to moderate, however, 46% galantamine-treated patients reported gastrointestinal AEs vs 25% donepezil patients.

Conclusions Physician and caregiver ease of use/satisfaction scores, and assessments of cognition and ADL, showed significant benefits for donepezil compared with galantamine in this direct comparative trial. Both treatments were well tolerated, with more gastrointestinal AEs reported for galantamine vs donepezil. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — Alzheimer's disease; cholinesterase inhibitors; donepezil; galantamine; direct comparative trial; ease of use

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, the most common cause of

dementia in elderly people, and a major cause of morbidity and mortality. AD is associated with a loss of cholinergic neurotransmission (Davies and Maloney, 1976; Perry *et al.*, 1977; Coyle *et al.*, 1983; Giacobini, 1990; Beach *et al.*, 2000), and, as a result of clinical trials showing dose-related clinical benefits, cholinesterase (ChE) inhibitors have become the mainstay for the treatment of patients with mild to moderate AD.

Donepezil is a chemically distinct, piperidine-based compound, and a highly specific, reversible

*Correspondence to: Prof. R. W. Jones, Research Institute for the Care of the Elderly, St Martin's Hospital, Bath, BA2 5RP, UK. Tel: +44 (0)1225 835866. Fax: +44 (0)1225 840395. E-mail: r.w.jones@bath.ac.uk

Contract/grant sponsors: Eisai Inc., Teaneck, NJ, USA; Pfizer Global Pharmaceuticals, Pfizer Inc., NY, USA.

inhibitor of acetylcholinesterase (AChE). Its long half-life allows once-daily administration. Significant benefits in cognition, global function, behaviour and activities of daily living (ADL), have been demonstrated in double-blind, placebo-controlled studies of up to one year in duration (Rogers *et al.*, 1996; Rogers *et al.*, 1998a; Rogers *et al.*, 1998b; Burns *et al.*, 1999; Feldman *et al.*, 2001a; Mohs *et al.*, 2001; Winblad *et al.*, 2001). The recommended dosing regimen is to start treatment at the clinically effective dose of 5 mg once daily for 4–6 weeks, followed by a one-step dose escalation to 10 mg once daily if clinically indicated. Overall, studies have demonstrated good tolerability and low discontinuation rates with donepezil. Adverse events (AEs) associated with donepezil use were generally mild, transient, cholinergic-induced and gastrointestinal in nature (Rogers *et al.*, 1998a; Rogers *et al.*, 1998b; Burns *et al.*, 1999).

Galantamine is a tertiary alkaloid compound and a reversible selective inhibitor of AChE. In randomised, placebo-controlled trials of up to six months' duration, galantamine demonstrated significant benefits in cognition, global function and ADL in patients with AD (Raskind *et al.*, 2000; Tariot *et al.*, 2000; Wilcock *et al.*, 2000). The relatively short half-life of galantamine requires twice-daily administration. Patients on galantamine begin treatment on 4 mg twice daily for 4 weeks, following which the dose is increased to a clinically effective dose of 8 mg twice daily; after an additional 4 weeks, the dose can be increased to 12 mg twice daily. Based on data from clinical trials referred to in the product labelling (Reminyl[®] [galantamine HBr] US package insert, 2001), there were no statistically significant differences between the 8 mg and 12 mg twice-daily doses of galantamine in their effects on cognition scores. AEs reported in clinical trials of galantamine were primarily gastrointestinal symptoms, with the majority reported as mild in severity (Raskind *et al.*, 2000; Tariot *et al.*, 2000; Wilcock *et al.*, 2000).

It is difficult to compare the efficacy and tolerability of ChE inhibitors across clinical trials due to differences in study design, patient baseline characteristics (such as disease severity, comorbid conditions and concomitant medication use), dosing regimens, and methods used to assess efficacy and safety. Consequently, if the drugs are to be compared, direct study of the two drugs in the same patient cohort within a clinical trial is necessary and desirable. A 52-week, open-label, rater-blinded, comparative study of galantamine and donepezil in patients with AD was recently published (Wilcock *et al.*,

2003). The population studied had moderate AD, with an inclusion range of 9–18 on the Mini-Mental State Examination (MMSE; Folstein *et al.*, 1975). The results did not demonstrate statistical differences between the two treatments at endpoint on the primary (ADL using Bristol Activities of Daily Living Scale) and secondary efficacy measures (cognition using MMSE and Alzheimer's Disease Assessment Scale—cognitive subscale [ADAS-cog; Rosen *et al.*, 1984]; and behaviour using the Neuropsychiatric Inventory [NPI]). Both treatments were well tolerated although the reported rates of the most common AEs among galantamine-treated patients (nausea, agitation, vomiting, headache and fall) tended to be higher than those for donepezil-treated patients (Wilcock *et al.*, 2003).

The primary objective of the current study was to directly compare ease of use, tolerability, and compliance using the highest recommended doses of donepezil and galantamine in patients with mild to moderate AD. Secondary objectives were to explore the effect of these two AChE inhibitors on cognition and ADL. In order to assess the ease of use of these two treatments, which differ in dosing frequency and dose escalation schedules, the study medications were administered open-label. However, the cognitive assessments were performed by independent raters blinded to study medication, dosing regimen, and to AEs. In order that the study reflected everyday clinical practice, dose adjustments based on tolerability were permitted throughout the study in accordance with the respective product labellings.

METHODS

Patients

Patients of at least 50 years of age diagnosed with probable or possible, mild or moderate AD consistent with NINCDS-ADRDA (McKhann *et al.*, 1984) and DSM-IV (American Psychiatric Association, 1994) criteria, and who met all other protocol criteria, were enrolled from a total of 14 centres in the UK, Finland, Germany and Norway. Patients were required to have a MMSE score at screening within the range of 10–24 inclusive. Results of a CT or MRI scan (within the past 18 months) were to be consistent with the diagnosis of AD. A caregiver, able to provide information on the patient's status and ensure patient compliance with treatment and clinic visits, was required for inclusion.

Patients treated previously with ChE inhibitors were excluded, as were patients with a known hypersensitivity to ChE inhibitors, piperidine or alkaloid

derivatives and those who had been treated with any investigational drug within 30 days of the screening visit. Patients taking medications with pronounced anticholinergic effects, such as drugs for Parkinson's disease, neuroleptics, or tricyclic antidepressants within 1 month of study entry were also excluded. Patients were similarly not enrolled if they had clinically significant obstructive pulmonary disease, asthma, gastrointestinal, endocrine, or cardiovascular disease.

The study was conducted in accordance with the Declaration of Helsinki and its amendments, or with the laws and regulations of the country in which the study was conducted, whichever afforded greater protection to the patient. Written informed consent was obtained from the patient and caregiver/legal representative. Verbal assent was obtained from patients unable to give written consent. The protocol, amendment, and informed consent form were approved by the Independent Ethics Committees of the respective study centres.

Study design

This was a 12-week, randomised, multicentre, open-label clinical trial. Patients were randomised via a computer-generated schedule to receive either donepezil or galantamine according to a 1:1 ratio. Patients were further stratified based on disease severity at screening, i.e. mild (MMSE scores of 19–24 inclusive) and moderate dementia (MMSE scores of 10–18 inclusive).

Donepezil and galantamine were administered orally, and titrated to maximum effective therapeutic doses, according to the respective approved product labelling (Aricept[®] [donepezil hydrochloride tablets] US package insert, 2000; Reminyl[®] [galantamine HBr] US package insert, 2001). Patients randomised to donepezil received 5 mg once daily for 4 weeks, after which the dosage was increased to 10 mg once daily. Patients randomised to galantamine began treatment on 4 mg twice daily. The dose of galantamine was increased to 8 mg twice daily after 4 weeks, and then, after a further 4 weeks, to 12 mg twice daily. The protocol allowed flexibility in dosing such that if the current dose was not tolerated, the dose of either drug could be decreased to the previous dose at any time. Subsequently, the dose could again be increased, with the intent to reach and maintain the highest recommended dose.

Outcome assessments

Primary outcome measures. The primary outcome measures were the Physician's and the Caregiver's

Satisfaction Questionnaires. Physicians and caregivers rated the ease of use and their satisfaction with the dosing frequency and titration of the assigned treatment for each patient by completing these questionnaires at weeks 4, 8, and 12. The Physician's Satisfaction Questionnaire consisted of six questions (total score range 6–30) and the Caregiver's Satisfaction Questionnaire comprised eight questions (total score range 8–40) with higher scores indicating greater satisfaction. Questions were designed to address the relevant issues facing physicians and caregivers in their use of ChE inhibitor therapy. These tests were previously used in a study of a similar design, (Wilkinson *et al.*, 2002) and were developed by the Clinical and Outcomes Research Group at Pfizer Inc. and Eisai Inc. in conjunction with external consultant, Dr Jean Endicott (Columbia University, New York City, NY, USA). In that study, a differential pattern of ratings was given by physicians and caregivers of patients treated with donepezil or rivastigmine, where ratings were consistent with the differences in titration, dosing regimen and tolerability of these two cholinesterase inhibitors, supporting the validity of the questionnaires.

Secondary outcome measures. Secondary efficacy assessments consisted of two measures of cognition: the ADAS-cog; and the MMSE; and one measure of functional ability: the Disability Assessment for Dementia (DAD) scale (Feldman *et al.*, 2001b). Results from the standard 11-item ADAS-cog and the modified 13-item ADAS-cog are reported. The modified 13-item ADAS-cog (Mohs, 1994) has a score range of 0–85 and includes two items, delayed recall and concentration/distractibility, in addition to those comprising the traditional, well-established 11-item ADAS-cog.

Cognitive assessments were carried out at screening, baseline, and at weeks 4, 8, and 12 by independent raters who were blinded to the patients' assigned study medication and dosing regimen, and other study information such as AEs. Separate case report forms were used by these raters to maintain blinding of assigned treatment.

The 40-item DAD scale was completed by a trained rater/physician, with caregiver input, to assess both instrumental and basic ADL, and total scores range from 0–40, with lower scores indicating greater impairment of ADL. The DAD assesses each ADL on three aspects of executive function: initiation (consisting of the ability to decide and/or start an action), planning and organization, and effective performance (consisting of the ability to complete an action).

Safety and tolerability

Safety and tolerability were evaluated by comparing treatment groups with respect to physical examination findings, changes in vital signs, ECG findings, laboratory test abnormalities, concomitant medication use, and compliance with study medication, as well as the monitoring of AEs throughout the study.

Clinical laboratory assessments included liver function tests, kidney function tests, haematological tests, and routine urinalysis. Treatment-emergent abnormal laboratory values (TEAVs) were defined as clinically significant values outside the normal range during treatment that were normal pre-treatment, or clinically significant exacerbations of pre-existing abnormal laboratory values. An AE was defined as any undesirable effect experienced by a patient during the trial, whether or not it was considered to be related to treatment. A serious adverse event (SAE) was defined as any AE that was life threatening or resulted in death, hospitalisation, prolongation of hospitalisation, or significant disability.

Statistical analysis

Determination of the overall study sample size was based on the total scores for the Physician's and Caregiver's Satisfaction Questionnaires. To have an 80% chance of detecting a difference of two points between treatment groups on both parameters, with an overall Type I error of 5%, 60 patients in each group were required.

The primary analyses were the total scores of the Physician's and Caregiver's Satisfaction Questionnaires at endpoint (week 12 last observation carried forward [LOCF] for the intent-to-treat [ITT] population). An analysis of variance (ANOVA) model was used to estimate and test the treatment differences. Observed cases (OC) analyses were performed for the ITT population at each scheduled visit (weeks 4, 8, and 12). In addition, treatment groups were compared for individual items of the Physician's and Caregiver's Satisfaction Questionnaires using the Cochran-Mantel-Haenszel test.

Comparisons between study groups were performed for the secondary efficacy assessments using analysis of covariance (ANCOVA) models with terms for treatment, centre/country and baseline (weeks 4, 8, and 12 OC, and week 12 LOCF). The response rates based on the 11-item and the 13-item ADAS-cog scores were compared using the Cochran-Mantel-Haenszel test. All statistical tests were two-tailed and performed at the 0.05 significance level

using SAS software, Version 6.12 (SAS Institute Inc., Cary, NC, USA). The safety data (including AEs) were summarized and no statistical tests were conducted.

RESULTS

Patient demographics

A total of 64 and 56 patients, respectively, were randomised to the donepezil and galantamine treatment groups. The majority of patients were enrolled at centres in the UK (46 patients, 38.3%) and Finland (44 patients, 36.7%). Patient demographics at screening and baseline are presented in Table 1. Treatment groups were similar for age and disease severity. Gender distribution did differ between the treatment groups: 51.6% of the donepezil treatment group were women compared with 71.4% in the galantamine

Table 1. Summary of patient demographics and characteristics at screening and baseline

| | Number of subjects | |
|--|---------------------------|---------------------------|
| | Donepezil (n = 64) | Galantamine (n = 56) |
| Mean age, years \pm SD (range) | 73.8 \pm 7.4 (51–88) | 75.1 \pm 7.7 (53–89) |
| Mean age at onset of diagnosis, years \pm SD (range) | 73.5 \pm 7.5 (51–88) | 74.6 \pm 7.9 (51–89) |
| Months since diagnosis, median (range) | 3.1 (0–47.5) | 3.2 (0–45.6) |
| Female (%) | 33 (51.6%) | 40 (71.4%) |
| Mean screening MMSE \pm SD* (range) | 17.9 (3.3) (11–24) | 18.1 (3.2) (10–25) |
| No. patients with screening MMSE scores (%)* | | |
| mild (19–24) | 27 (42.1) | 26 (46.4) |
| moderate (10–18) | 37 (57.8) | 27 (48.2) |
| Mean baseline MMSE score \pm SD (range)** | 18.3 (3.3) (8–24) | 18.4 (3.7) (10–25) |
| Mean baseline ADAS-cog (11-item) \pm SD (range) | 23.1 (7.4) (8–42) | 23.1 (8.7) (10–44) |
| Mean baseline ADAS-cog (13-item) \pm SD (range) | 32.5 (8.2) (16–54) | 32.8 (9.9) (17–56) |
| Mean baseline DAD Total score \pm SD (range) | 25.9 (9.7) (3–40) | 25.4 (10.7) (0–40) |

*At screening, the MMSE was not administered to three patients in the galantamine group; one patient had an MMSE score of 25.

**At baseline, one patient in the donepezil group had an MMSE score of 8, and one patient in the galantamine group had an MMSE score of 25.

treatment group ($p = 0.03$). All patients had screening MMSE scores of 10–24, as required by the protocol, with the exception of one patient with a screening score of 25 (baseline score of 23). Two patients had baseline MMSE scores outside the 10–24 range: one patient with a score of 8 (screening score of 11), and one patient with a score of 25 (screening score of 23).

Vital signs were normal at baseline except for slight elevations in median systolic blood pressure (donepezil, 141 mm Hg; galantamine, 140 mm Hg) that remained slightly elevated throughout the study. No clinically important treatment differences were observed in past or present medical history findings, or in the proportions of patients who had taken medications prior to the start of the study (donepezil group, 70.3%; galantamine, 78.6%), or who received concomitant medication during the study (donepezil, 82.8%; galantamine, 91.1%). No clinically meaningful differences in treatment-emergent concomitant medication use during the study were identified.

Disposition

Of the 120 patients who received study medication, 61 (95.3%) patients in the donepezil group and 51 (91.1%) in the galantamine group completed the study. Three (4.7%) donepezil and four (7.1%) galantamine patients discontinued prematurely due to AEs. These AEs were considered to be related to study drug in one donepezil patient (depression) and three galantamine patients (depression, vomiting, nausea). AEs considered unrelated to study drug resulted in discontinuation in two (3.1%) patients in the donepezil group, and one (1.8%) patient in the galantamine group. Subject default resulted in one discontinuation in the galantamine group.

Compliance and dosing

Overall, patients took the study drugs as prescribed by the clinician, and in general, patients in both treatment groups took their daily doses as directed. The maximum daily doses of donepezil (10 mg once daily) and galantamine (12 mg twice daily) were administered in 98.4% and 94.6% of patients in these groups, respectively, at some point in the study (Table 2). However, more patients receiving donepezil remained at the maximum dose at the end of the study or at last study visit, compared with galantamine (92.2% vs 71.4%, respectively).

Patients were permitted to return for unscheduled visits following clinic visits at weeks 4 and 8 in the event that a dose escalation was not tolerated. From

Table 2. Number of patients in each donepezil and galantamine dosing regimen throughout the study

| Donepezil ($n = 64$) | | Galantamine ($n = 56$) | |
|------------------------|-----------|--------------------------|-----------|
| mg/day | n (%) | mg/day | n (%) |
| Always on 5 | 1 (1.6) | Always on 8 | 1 (1.8) |
| 5 → 10 | 58 (90.6) | 8 → 16 | 2 (3.6) |
| 5 → 10 → 5 | 4 (6.3) | 8 → 16 → 24 | 40 (71.4) |
| 5 → 10 → 5 → 10 | 1 (1.6) | 8 → 16 → 24 → 16 | 13 (23.2) |

weeks 4 to 8 there was no significant difference between the two treatment groups regarding the number of patients requiring unscheduled visits (3 donepezil vs 0 galantamine). However, from weeks 8 to 12, significantly more galantamine patients required unscheduled visits (0 donepezil vs 13 galantamine; $p = 0.0001$). Overall, only three (4.7%) patients in the donepezil group had unscheduled visits due to dose tolerability problems compared with 13 (23.2%) in the galantamine group ($p < 0.01$).

Satisfaction/Ease of use

The total mean score for the Physician's Satisfaction Questionnaire showed statistically significant greater satisfaction/ease of use for the donepezil group compared with the galantamine group at week 4 (OC), week 12 (OC) and endpoint (week 12 LOCF; Figure 1A). Responses to four of the six individual items of the Physician's Satisfaction Questionnaire

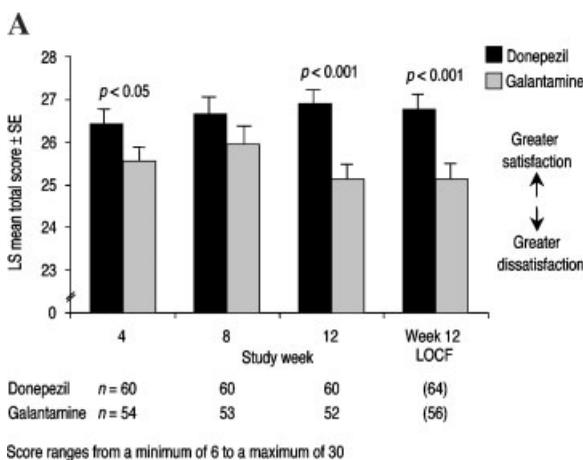


Figure 1A. Physician's Satisfaction/Ease of Use Questionnaire Total Score (ITT population)

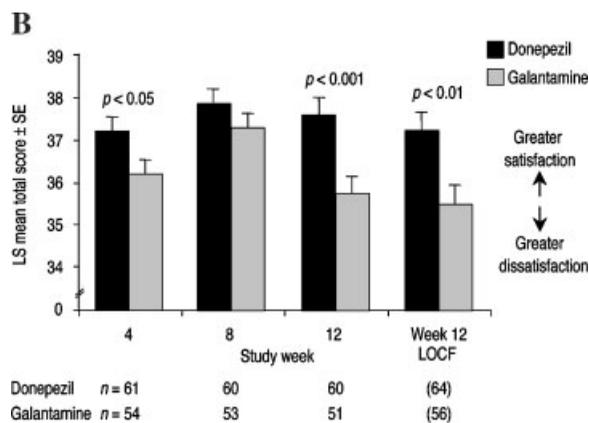


Figure 1B. Caregiver's Satisfaction/Ease of Use Questionnaire Total Score (ITT population)

at endpoint favoured donepezil over galantamine ($p < 0.01$) as follows: frequency of phone calls/visits concerning use of study medication and side effects, dosing frequency, titration schedule to clinically effective dose, and overall convenience of use. For the remaining two items (ease of use for the patient and caregiver, overall satisfaction with medication), the responses favoured donepezil but were not statistically significant.

The total mean score for the Caregiver's Satisfaction Questionnaire also revealed statistically significant greater satisfaction/ease of use for the donepezil treatment group compared with the galantamine group at weeks 4 (OC) and 12 (OC) and endpoint (week 12 LOCF; Figure 1B). Responses to three of the eight individual items (i.e. satisfaction with dosing frequency, tolerating the medication, and physician contact about side effects) at endpoint showed statistical significance in favour of donepezil ($p < 0.05$). For the remaining five items, the responses favoured donepezil over galantamine, but were not statistically significant.

Cognition

Significantly greater improvement in cognition was observed for donepezil compared with galantamine for the 11-item ADAS-cog (Figure 2) and the 13-item modified ADAS-cog at week 12 and at endpoint ($p < 0.05$). At weeks 4 and 8 the trend favoured donepezil. Significantly greater improvement in cognition was also observed for donepezil compared with galantamine for the MMSE at endpoint ($p < 0.05$; Figure 3).

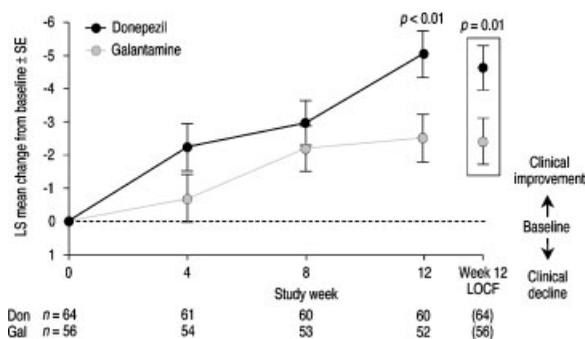


Figure 2. LS mean change from baseline in ADAS-cog (11-item) assessed by independent raters blind to treatment (ITT population)

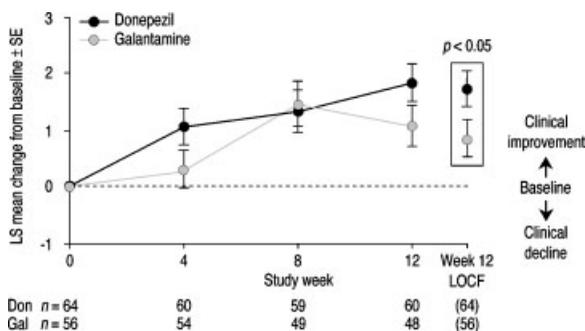


Figure 3. LS mean change from baseline in MMSE assessed by independent raters blind to treatment (ITT population)

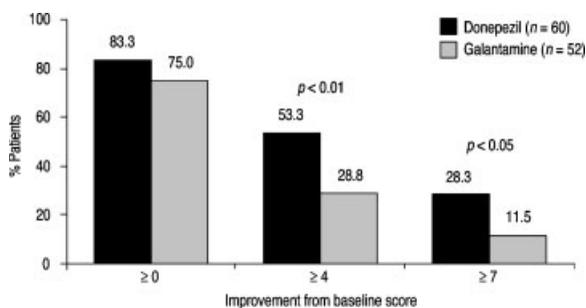


Figure 4. Degree of response on the ADAS-cog (11-item) at Week 12 (OC)

The percentage of patients showing a substantial response on the 11-item ADAS-cog, with improvement of at least seven points from baseline at week 12 (OC), was donepezil 28.3% vs galantamine 11.5% ($p = 0.029$), and the percentage of patients showing a good response, with improvement of at least four points, was donepezil 53.3% vs galantamine 28.8% ($p = 0.009$; Figure 4). Similar findings were observed for the 13-item ADAS-cog.

Further post-hoc analyses were conducted to explore whether the 30% of galantamine patients who could not tolerate 24 mg/day influenced the observed difference in ADAS-cog scores between the donepezil and galantamine groups. When analyses of treatment effects at Week 12 (OC) were performed, stratified by dose of drug, patients treated with 10 mg/day of donepezil showed a greater improvement on the 11-item ADAS-cog (LS mean treatment difference 2.49; $p < 0.05$), and the 13-item ADAS-cog (LS mean treatment difference 2.78; $p < 0.05$), than galantamine patients receiving 24 mg/day.

Functional ability

When assessed by total score on the DAD scale, significantly greater improvement in ADL was observed at weeks 4, 12, and endpoint for donepezil compared with galantamine ($p < 0.05$; Figure 5). In patients receiving galantamine, the total DAD scores remained below baseline throughout the study. At endpoint, the mean changes from baseline favoured donepezil compared with galantamine for nine out of ten individual items on the DAD. In the case of two of these individual items (meal preparation, and finance and correspondence), patients receiving donepezil showed significantly greater improvements compared with those receiving galantamine ($p < 0.05$ and $p = 0.001$, respectively).

Tolerability and safety

Treatment-emergent AEs (all causalities) were experienced by 43 (67.2%) donepezil patients and 41 (73.2%) galantamine patients. The most frequent treatment-emergent AEs were nausea, diarrhoea, anor-

Table 3. Treatment-emergent AEs occurring in $\geq 5\%$ of patients (all causalities)

| | Number of subjects (%) | |
|--------------------------|-------------------------------|---------------------------------|
| | Donepezil (<i>n</i> = 64) | Galantamine (<i>n</i> = 56) |
| Nausea | 10 (15.6) | 13 (23.2) |
| Diarrhoea | 6 (9.4) | 8 (14.3) |
| Anorexia | 3 (4.7) | 5 (8.9) |
| Vomiting* | 0 (0.0) | 7 (12.5) |
| Headache | 4 (6.3) | 3 (5.4) |
| Urinary tract infection* | 2 (3.1) | 4 (7.1) |
| Dizziness* | 1 (1.6) | 3 (5.4) |

*AEs occurring at twice the rate or more in the comparator group.

exia, vomiting, headache, urinary tract infection, and dizziness (Table 3). The incidence of gastrointestinal AEs, including nausea, vomiting, and diarrhoea, was higher in the galantamine group (46.4%) compared with the donepezil group (25.0%). More patients taking galantamine (21.4%) reduced their dose or temporarily discontinued medication due to AEs than patients taking donepezil (9.4%).

More than 95% of AEs experienced were mild to moderate in nature. Serious AEs were experienced by four patients (6.3%) in the donepezil group (congestive heart failure, abscess, skin disorder, atrial fibrillation and hyponatraemia), and two patients (3.6%) in the galantamine group (heart failure and hypotension). However, none of these were considered by the investigator to be drug related.

Cardiovascular effects were similar for both treatment groups, with no clinically significant abnormal changes in heart rate. Few treatment-emergent abnormal physical findings or laboratory abnormalities were observed in the two groups; no clinically meaningful differences were found between the two treatments, and no patients discontinued due to laboratory abnormalities or physical findings in either group.

DISCUSSION

In this direct comparative clinical trial of donepezil and galantamine, an open-label study design was necessary in order to compare ease of use and satisfaction for treatments having different dosing regimens. Dosing was consistent with approved product labelling, and donepezil and galantamine were titrated to maximum effective therapeutic doses while allowing dosing flexibility to enhance tolerability, as reflects routine clinical practice. To minimize the potential impact of

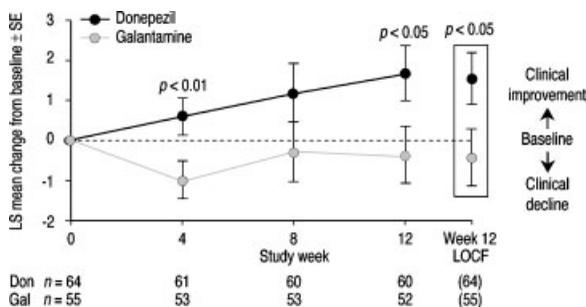


Figure 5. LS mean change from baseline in DAD total score (ITT population)

open-label treatment on the assessment of cognition, the ADAS-cog and MMSE were administered by independent raters who were blind to treatment, dosing regimen and other outcome information such as AEs. The two treatment groups were similar at baseline except for a significant difference in gender distribution. Further analyses not reported here on the ADAS-cog, MMSE and DAD indicated that there were no treatment-by-gender interactions.

Physicians and caregivers completed questionnaires in which they were asked about their satisfaction with the study medication, primarily with regard to ease of use in daily practice. Physicians may have had clinical experience with both donepezil and galantamine and, it could be argued, be potentially open to bias; however, caregivers assessed their satisfaction with only the specific treatment that the patient received, and should therefore be less liable to bias. Both physicians and caregivers reported significantly higher total satisfaction/ease of use scores with donepezil compared with galantamine at weeks 4 and 12 and at study endpoint. Responses at endpoint to all six individual questions on the Physician's Satisfaction Questionnaire and all eight questions on the Caregiver's Satisfaction Questionnaire favoured donepezil over galantamine.

Significantly greater improvements in cognition were observed for donepezil for the 11-item ADAS-cog, the 13-item modified ADAS-cog, and the MMSE, compared with galantamine. The degree of response, as measured by the 11-item and 13-item ADAS-cog, showed that in both treatment groups, approximately 75% patients showed either no change, or an improvement, in ADAS-cog score at week 12. However, both the percentage of patients showing an improvement of at least four points, and the percentage showing an improvement of at least seven points, were significantly higher in the donepezil cohort compared with the galantamine cohort.

In addition, donepezil treatment resulted in significantly greater benefit (either more improvement or less decline) in ADL than galantamine, based on the DAD total score and the DAD individual items. The improvement from baseline in DAD total score in the donepezil group is an interesting finding, as in controlled clinical trials with ChE inhibitors, ADL tend to be maintained at around baseline levels after 12 weeks. It is difficult to determine the reasons for this marked difference between the two compounds on the DAD scale. Although raters and caregivers were not blinded to treatment for the DAD, it should be noted that the significant benefits for donepezil over galantamine were consistent across all efficacy measures in

this study, regardless of whether raters were blinded or not, suggesting a real treatment difference.

Both treatments were well tolerated, with few patients discontinuing from the study due to AEs in either study arm. However, twice as many patients reported gastrointestinal AEs (including nausea, vomiting and diarrhoea) in the galantamine group compared with the donepezil group. Furthermore, galantamine was associated with more reductions in dose, or temporary discontinuation of medication due to AEs, than donepezil. Dose adjustments resulted in significantly more unscheduled office visits for galantamine patients than donepezil patients. Fewer galantamine-treated patients (71%) could be maintained at the maximum dose compared with donepezil (92%).

The greater observed benefits of donepezil over galantamine reported here may raise the question of whether the delay in reaching a clinically effective dose and/or the final tolerated dose taken by the patient has any implications for the overall treatment response to galantamine. To improve tolerability, the recommended dose titration for galantamine requires a four-week delay in reaching a clinically effective dose, and it could be argued that this may have contributed to a reduced overall treatment response seen in patients on galantamine. Additionally, approximately 30% of patients in the galantamine group were unable to remain at the maximum therapeutic dose of 24 mg/day. Although this could have contributed to a reduced response in patients taking galantamine treatment, no differences were observed in the ADAS-cog mean scores at week 12 between patients receiving 16 mg/day and 24 mg/day galantamine, consistent with a previous trial with a larger number of participants (Tariot *et al.*, 2000). Furthermore, the improvements in ADAS-cog were significantly better at week 12 for patients receiving 10 mg/day donepezil than for patients receiving 24 mg/day galantamine.

In summary, physician and caregiver ease of use/satisfaction scores and assessments of both cognition and ADL all showed significant benefits for donepezil compared with galantamine. The benefits for donepezil were consistent across all efficacy endpoints, and across different assessors and raters. Both treatments were well tolerated but fewer gastrointestinal AEs were reported for the donepezil group compared with galantamine in this first reported head-to-head study of the two AChE inhibitors. These factors are important to consider when physicians and caregivers are making decisions concerning choice of agent in the treatment of mild to moderate AD.

KEY POINTS

- In this head-to-head, open-label, direct comparison study of donepezil and galantamine in patients with mild to moderate AD, significant benefits were observed for donepezil over galantamine on all efficacy measures.
- Physician and caregiver overall satisfaction and ease of use of treatment was significantly higher in the donepezil group compared with galantamine.
- Significantly greater improvements were also seen on blinded-rater assessments of cognition and investigator-rated assessments of activities of daily living for donepezil vs galantamine.
- Both treatments were well tolerated, but more gastrointestinal AEs were seen in the galantamine group vs the donepezil group.

ACKNOWLEDGEMENTS

The authors would like to thank the following contributors to the conduct or design of this study: Georg Adler, Zentralinstitut für Seelische Gesundheit, Mannheim, Germany; Kari Alhainen, Memory Research and Treatment Centre Suinuu, Joensuu, Finland; Roger Bullock, Kingshill Research Centre, Victoria Hospital, Swindon, UK; Lynn Burger, Pfizer Inc., New York, USA; Timo Erkinjuntti, Memory Research Unit, Helsinki University, Finland; Merja Hallikainen, Kuopio University Hospital, Kuopio, Finland; John Ieni, Eisai Inc., Teaneck, New Jersey, USA; Wolfgang Kafferlein, Bamberg, Germany; Jürgen Kohler, Emmendingen, Germany; Anne Koviisto, Kuopio University Hospital, Kuopio, Finland; Torgeir Lindvig, Sem, Norway; Stanley Martin, Memory Assessment Clinic, Bradford, UK; Robert Smith, Memory Assessment Clinic, Bradford, UK; Sven Peter Wetterberg, Medi 3 AS, Aalesund, Norway.

This study was sponsored by Eisai Inc., Teaneck, New Jersey, USA, and Pfizer Global Pharmaceuticals, Pfizer Inc., New York, USA.

REFERENCES

American Psychiatric Association. 1994. *Diagnostic and Statistical Manual of Mental Health Disorder, 4th edition, revision. (DSM-IV-R)*. American Psychiatric Association: Washington, DC.

Aricept[®] (donepezil hydrochloride tablets). December 2000, US package insert. Eisai Inc., Teaneck, New Jersey, USA.

- Beach TG, Kuo Y-M, Spiegel K, *et al.* 2000. The cholinergic deficit coincides with A β deposition at the earliest histopathologic stages of Alzheimer disease. *J Neuropathol Exp Neurol* **59**: 308–313.
- Burns A, Rossor M, Hecker J, *et al.* 1999. The effects of donepezil in Alzheimer's disease—results from a multinational trial. *Dement Geriatr Cogn Disord* **10**: 237–244.
- Coyle JT, Price DL, DeLong MR. 1983. Alzheimer's disease: a disorder of cortical cholinergic innervation. *Science* **219**: 1184–1190.
- Davies P, Maloney AJF. 1976. Selective loss of central cholinergic neurons in Alzheimer's disease. *Lancet* **2**: 1403.
- Feldman H, Gauthier S, Hecker J, *et al.* 2001a. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology* **57**: 613–620.
- Feldman H, Sauter A, Donald A, *et al.* 2001b. The disability assessment for dementia scale: a 12-month study of functional ability in mild to moderate severity Alzheimer disease. *Alzheimer Dis Assoc Disord* **15**: 89–95.
- Folstein MF, Folstein SE, McHugh PR. 1975. 'Mini-Mental State'. A practical method for grading the cognitive state of subjects for the clinician. *J Psychiatr Res* **12**: 189–198.
- Giacobini E. 1990. The cholinergic system in Alzheimer's disease. *Prog Brain Res* **84**: 321–332.
- McKhann G, Drachman D, Folstein M, *et al.* 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services task force in Alzheimer's disease. *Neurology* **34**: 939–944.
- Mohs RC. 1994. *Adapted from the modified (by Connor and Schafer) Administration and Scoring Manual for the Alzheimer's Disease Assessment Scale, Revised Edition*. Copyright Mount Sinai School of Medicine: New York.
- Mohs RC, Doody RS, Morris JC, *et al.* 2001. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology* **57**: 481–488.
- Perry EK, Perry RH, Blessed G, Tomlinson BE. 1977. Necropsy evidence of central cholinergic deficits in senile dementia. *Lancet* **1**: 189.
- Raskind MA, Peskind ER, Wessel T, Yuan W. 2000. Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. *Neurology* **54**: 2261–2268.
- Reminyl[®] (galantamine HBr). March 2001, US package insert. Janssen, Titusville, New Jersey, USA.
- Rogers SL, Friedhoff LT and The Donepezil Study Group. 1996. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US multicenter, randomized, double-blind, placebo-controlled trial. *Dementia* **7**: 293–303.
- Rogers SL, Doody RS, Mohs RC, Friedhoff LT and The Donepezil Study Group. 1998a. Donepezil improves cognition and global function in Alzheimer's disease: a 15-week, double-blind, placebo-controlled study. *Arch Int Med* **158**: 1021–1031.
- Rogers SL, Farlow MR, Doody RE, Mohs RC, Friedhoff LT. 1998b. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* **50**: 136–145.
- Rosen WG, Mohs RC, Davis KL. 1984. A new rating scale for Alzheimer's disease. *Am J Psychiatry* **141**: 1356–1364.
- Tariot PN, Solomon PR, Morris JC, *et al.* 2000. A 5-month, randomized, placebo-controlled trial of galantamine in AD. *Neurology* **54**: 2269–2276.

- Wilcock GK, Lilienfeld S, Gaens E (on behalf of the Galantamine International-1 Study Group). 2000. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomized controlled trial. *BMJ* **321**: 1445–1449.
- Wilcock G, Howe I, Coles H, *et al.* 2003. A long-term comparison of galantamine and donepezil in the treatment of Alzheimer's disease. *Drugs Aging* **20**: 777–789.
- Wilkinson DG, Passmore AP, Bullock R, *et al.* 2002. A multinational, randomized, 12-week comparative study of donepezil and rivastigmine in patients with mild to moderate Alzheimer's disease. *Int J Clin Prac* **56**: 441–446.
- Winblad B, Engedal K, Soininen H, *et al.* 2001. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology* **57**: 489–495.