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Efficacy of rivastigmine in subjects with moderately severe Alzheimer's disease

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SUMMARY

Background Cholinesterase (ChE) inhibitors are primarily used in the treatment of mild to moderate Alzheimer's disease (AD), but may also be effective in more severe disease.
Objective To evaluate the dual ChE inhibitor, rivastigmine, in more severe dementia.
Methods We retrospectively analysed pooled data from three randomised, placebo-controlled, double-blind, 6-month trials, involving 2126 AD subjects. Subjects were selected according to baseline Mini-Mental State Examination (MMSE) score to identify subjects with more severe cognitive impairment (10–12 MMSE points). One-hundred-and-seventeen subjects were included who had been treated with rivastigmine 6–12 mg/day or placebo. The AD Assessment Scale-Cognitive Subscale (ADAS-Cog), the MMSE, a six-item subscore of the Progressive Deterioration Scale (PDS) and the BEHAVE-AD assessed efficacy. Tolerability was assessed by recording adverse events (AEs) and the relative risk (RR) of discontinuation.
Results This group of subjects responded well to rivastigmine. After 6 months, the mean ADAS-Cog score declined by 6.3 points in the placebo group and increased by 0.2 points in the rivastigmine group (observed cases; $p < 0.001$). Clinical benefits were also observed with the MMSE, the six-item PDS score and items of the BEHAVE-AD. Rivastigmine showed the same pattern of AEs as in other studies, but the RR of dropping out due to AEs was lower than in subjects with milder AD.
Conclusion Current treatment guidelines do not recommend treating individuals with severe AD with ChE inhibitors. However, this retrospective analysis suggests that rivastigmine 6–12 mg/day may benefit subjects with more severe disease, as well as subjects with mild to moderate impairment. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — Alzheimer's disease; severe; cholinesterase inhibitors; rivastigmine; clinical trials; retrospective analysis

INTRODUCTION

Cholinesterase (ChE) inhibitors are currently a standard medical intervention for Alzheimer's disease (AD). Their clinical benefit is thought to derive primarily from an increase in synaptic acetylcholine (ACh) levels, leading to enhanced cholinergic neurotransmission, and alleviation of the debilitating symptoms in the key areas of dementia — activities of daily living (ADL), behaviour and cognitive performance (Grutzendler and Morris, 2001). Since the development of tetrahydroaminoacridine (tacrine), several other ChE inhibitors belonging to different chemical classes have emerged. They are either selective for inhibition of acetylcholinesterase (AChE) or dual inhibitors of both AChE and butyrylcholinesterase (BuChE). Donepezil, rivastigmine and galantamine have been shown to be effective in the treatment of AD (Trinh *et al*., 2003).

Although the basic efficacy of ChE inhibitors in AD is well established, knowledge of which patient characteristics predict a response to treatment remains limited. While the search for predictive factors is probably limited to some extent by heterogeneity in AD, evidence has arisen indicating that patients with moderate disease tend to respond more strongly to ChE inhibitor treatment than patients with mild

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disease (Schneider and Farlow, 1996; Kaufer *et al*., 1998). This observation raises the question of whether patients with more severe AD also respond positively to ChE inhibitor treatment. In many countries, it is not current clinical practice to administer ChE inhibitors in severe AD. In the UK, for instance, the National Institute for Clinical Excellence (NICE) currently recommends that patients with a Mini-Mental State Examination (MMSE) score of 12 or less should not receive treatment with these drugs (NICE, 2001).

Few studies to date have specifically investigated the use of ChE inhibitors in individuals with severe AD. Some reports, however, have indicated that they are indeed effective in this patient population (Farlow *et al.*, 2001; Feldman *et al.*, 2001; Doraiswamy *et al.*, 2002; Wilkinson *et al.*, 2002). It is generally accepted that patients with an MMSE score below 15 suffer from moderately severe to severe cognitive impairment. According to Folstein *et al.* (2000), a score of 10 points on the MMSE corresponds to the upper limit of the range defining severe cognitive impairment.

Rivastigmine tartrate (Exelon®) is a ChE inhibitor of the phenylcarbamate type that inhibits both AChE and BuChE (Weinstock, 1999). It shows preferential selectivity for the hippocampus and cortex (Enz *et al.*, 1993), those regions of the brain in which cholinergic deficits are most pronounced in AD (Arendt *et al.*, 1992). A number of phase III clinical trials have demonstrated that rivastigmine is effective in improving and sustaining ADL, behavioural and cognitive function in subjects with AD (Corey-Bloom *et al.*, 1998; Schneider *et al.*, 1998; Rösler *et al.*, 1999). These studies provided a data set of more than 2000 subjects in which specific questions about the response of different subgroups to rivastigmine treatment can be addressed. Analysis of this combined data set has demonstrated that subjects with at least moderate dementia, defined by an MMSE score of 17 or less, respond more strongly to rivastigmine treatment than subjects with milder dementia (Farlow *et al.*, in press). Further analysis has also determined that subjects with moderately severe or severe dementia, defined by a Global Deterioration Scale (GDS) score of five or more, responded more strongly to rivastigmine treatment than subjects with mild dementia (Doraiswamy *et al.*, 2002; Potkin *et al.*, 2002).

In the current analysis, we used pooled data from three large placebo-controlled studies to address the question of whether subjects with moderately severe dementia respond to treatment with rivastigmine. We considered the response of subjects to rivastigmine in terms of efficacy and safety/tolerability, analysing the magnitude of response relative to placebo.

METHODS

This was a retrospective statistical analysis of data derived from three 6-month, multicentre, double-blind, placebo-controlled, parallel-group studies (Corey-Bloom *et al.*, 1998; Schneider *et al.*, 1998; Rösler *et al.*, 1999) which investigated the effects of rivastigmine in subjects with probable AD. Subjects included in these Phase III trials were at least 50 years of age, fulfilled DSM-IV (APA, 1994) and NINCDS-ADRDA (McKhann *et al.*, 1984) criteria for AD, and had baseline MMSE scores between 10 and 26, inclusively.

Analysis of the pooled data set was justified, as the three trials included shared similar designs, inclusion criteria and dosage schedules. One of the three studies had four treatment arms comprising rivastigmine 3 mg/day, 6 mg/day, 9 mg/day or placebo (Schneider *et al.*, 1998). The remaining two studies had treatment arms comprising rivastigmine 1–4 mg/day, rivastigmine 6–12 mg/day or placebo (Corey-Bloom *et al.*, 1998; Rösler *et al.*, 1999). Another trial in the Phase III programme allowed free dosing within a range of 2–12 mg/day and differed in other respects from the current studies and could not be included in the current analysis. The dose of rivastigmine was up-titrated rapidly, at 1–2 week intervals depending on tolerability. In this report, we focus on the rivastigmine 6–12 mg/day treatment group as this corresponds with the proven effective and the currently recommended dose range for rivastigmine.

Selection of subjects with moderately severe AD

Selection of subjects according to baseline disease severity was carried out on the basis of the level of cognitive impairment according to MMSE score. The present analysis focuses on those subjects within the pooled sample who had the greatest cognitive impairment, i.e. MMSE scores between 10 and 12. As shown in Table 1, this corresponded to GDS scores of 4 and above ('moderately severe to severe dementia') in the vast majority of cases.

Efficacy assessments

Cognitive performance was measured using the 11-item ADAS-Cog scale (Rosen *et al.*, 1984) and the MMSE (Folstein *et al.*, 1975). ADLs were assessed using the Progressive Deterioration Scale (PDS) (DeJong *et al.*, 1989), a 29-item bipolar 100 mm analog scale completed by the subjects' caregiver. The PDS is highly redundant and contains mainly

Table 1. Demographic and clinical variables according to treatment group

	Rivastigmine 6–12 mg/day	Placebo
n	62	55
Mean age (years) (range)	72.4 (55–88)	73.6 (53–86)
Sex: Female (%)	77	67
Mean duration of dementia (months) (range)	47.8 (10–136)	45.4 (6–108)
GDS score $\geq$4 (moderately severe to severe) (%)	85	91
Mean ADAS-Cog score	43.4	44.5
Mean MMSE score	11.1	11.2
Mean PDS six-item score	43.6	41.2

instrumental ADL (IADL) items, i.e. activities that are increasingly difficult to perform as AD progresses (Potkin *et al.*, 2002). Thus, in order to reduce redundancy and to avoid a floor effect in these moderately severe to severe subjects, we identified six PDS items ($\sim$20% of the total PDS item pool) that showed the highest mean baseline scores, suggesting that these items represent the best maintained functions and could be considered the highest functional resource available to the subjects at baseline (Feldman *et al.*, 2003). The six items were:

- 'Has little or no difficulty in telling the time correctly'
- 'Always uses tools, household implements, etc. appropriate to the task'
- 'Can walk or move around safely and without getting lost in the immediate neighbourhood'
- 'Typically needs no help or advice to dress appropriately for climate and conditions'
- 'Good (proper) eating behaviour—uses proper utensils/manners, all/most of the time'
- 'Takes normal precautions in daily activities'

As described for the full (29-item) PDS, the score range for the six-item version is 0–100, calculated as the average score from all items included. Behavioural changes were evaluated using the BEHAVE-AD scale, which has 25 items in seven groups covering paranoid and delusional ideation, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbances and anxieties/phobias (Reisberg *et al.*, 1996). In the original studies (Corey-Bloom *et al.*, 1998; Schneider *et al.*, 1998; Rösler *et al.*, 1999) the BEHAVE-AD was not reported separately. It was used, together with other behavioural, cognitive and functional assessments, to evaluate global changes as expressed on the Clinicians Interview Based Impression of Change (CIBIC)-plus scale.

Safety/tolerability assessments

Safety and tolerability information were collated from the results of the trials, and stratified according to the severity of dementia at baseline and treatment administered. The relative risk (RR) of discontinuing from the study due to adverse events (AEs) was calculated.

STATISTICAL METHODS

Since raw data for all three studies were available, all analyses were carried out on the pooled dataset using study as a fixed effect or stratification factor. Analyses were performed in the observed cases (OC) and intent-to-treat, last-observation-carried-forward (ITT-LOCF) populations. The OC population represents all randomised subjects with an evaluation made while on study drug at designated assessment times. The ITT-LOCF population represents all randomised subjects with at least one evaluation made while being treated, with their last observations carried forward. The two data sets produced very similar results. For the BEHAVE-AD, only subjects with the symptom present at baseline were included, and therefore, only the OC analysis is presented. Three treatment groups (rivastigmine 1–4 mg/day, rivastigmine 6–12 mg/day and placebo) were analysed, but only comparisons between the 6–12 mg/day and the placebo group are reported. This is because the proven effective dose and the recommended dose range for rivastigmine is 6–12 mg/day.

Statistical analyses on the mean change from baseline in ADAS-Cog and six-item PDS cluster were performed using a two-way ANOVA model with treatment group and study as factors. Analyses on the mean change from baseline in MMSE score were performed using a van Elteren test. To compare the proportion of subjects in whom cognitive function

was sustained or improved using the ADAS-Cog, a Cochran-Mantel-Haenszel test (CMH test) blocking for study was used. This test was also used to compare the proportion of subjects showing improvement in behavioural symptoms between treatment groups.

RESULTS

Subject demographics

The demographic and clinical characteristics of subjects are summarised in Table 1.

A total of 117 subjects were identified, of whom 62 received rivastigmine 6–12 mg/day and 55 received placebo (Table 1). The demographic and clinical features of the treatment groups were well matched at baseline with no statistically significant differences between groups. Forty subjects (19 on rivastigmine, 21 on placebo) originated from the study by Rösler *et al.* (1999), 36 (23 on rivastigmine, 13 on placebo) from the study by Schneider *et al.* (1998) and 41 (20 on rivastigmine, 21 on placebo) from the study by Corey-Bloom *et al.* (1998). The mean dose of rivastigmine in treated subjects at the end of the study was approximately 9 mg/day.

EFFICACY OF RIVASTIGMINE TREATMENT

Cognitive function

ADAS-Cog. Rivastigmine had a positive effect on the rate of cognitive decline in subjects with severe AD (Figure 1). After 26 weeks, there was a small improvement (0.2 points) relative to baseline in the mean ADAS-Cog score of subjects treated with rivastigmine, whereas there was a mean decline of 6.3 points in subjects receiving placebo (OC population; $p < 0.001$). In the ITT-LOCF population there was no change from baseline in rivastigmine-treated subjects, compared with a decline of 6.1 points in the placebo group (treatment difference, $p < 0.001$).

The efficacy of rivastigmine was also assessed in terms of the proportion of subjects in whom cognitive function was sustained or improved from baseline after 6 months of treatment (mean change from baseline in ADAS-Cog ≥ 0). In total, 46% of the subjects treated with rivastigmine either improved or showed no deterioration, compared with 9% of subjects treated with placebo (OC population; $p < 0.001$; CMH test). The respective figures in the ITT-LOCF population were 44% for rivastigmine and 7% for placebo ($p = 0.001$).

MMSE. After 26 weeks, subjects treated with rivastigmine showed a mean change from baseline of −0.8 points on the MMSE, compared with −2.5 points in the placebo group (OC population; $p = 0.02$). The respective figures in the ITT-LOCF population were −0.8 and −2.5 points ($p = 0.02$).

ADL. Subjects on rivastigmine showed less decline of ADLs than those on placebo. In the placebo group, functioning declined by a mean of 6.5 points on the PDS six-item score after 6 months. In contrast, the mean decline among subjects treated with rivastigmine was 1.6 points (OC population; $p = 0.061$). In the ITT-LOCF population, the decline was 2.0 points for rivastigmine and 6.3 points for placebo ($p = 0.065$).

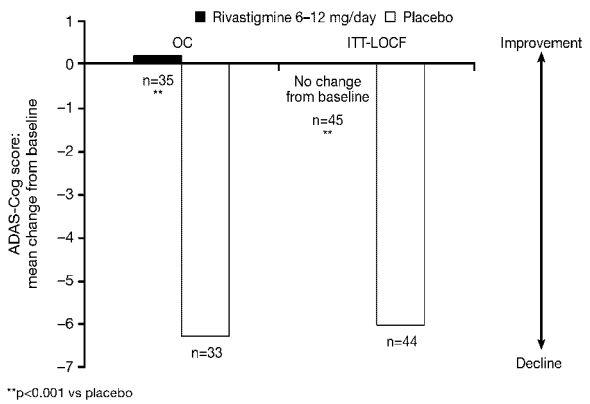

Figure 1. Cognitive performance: mean change from baseline in ADAS-Cog score

Behavioural symptoms

The most common behavioural symptoms occurring at baseline were activity disturbance (in 79.9% of all subjects) and anxieties/phobias (72.7%). Other symptoms recorded in more than half the subjects were aggressiveness (59.7%), paranoid and delusional ideation (58.3%) and affective disturbance (51.1%). Compared with placebo, subjects treated with rivastigmine showed a significant reduction in aggressiveness after 26 weeks (OC population; $p = 0.023$, subjects with symptoms present at baseline) (Figure 2). The reduction in the frequency of hallucinations among subjects treated with rivastigmine compared with placebo did not reach the 5% level of significance (OC population; $p = 0.063$).

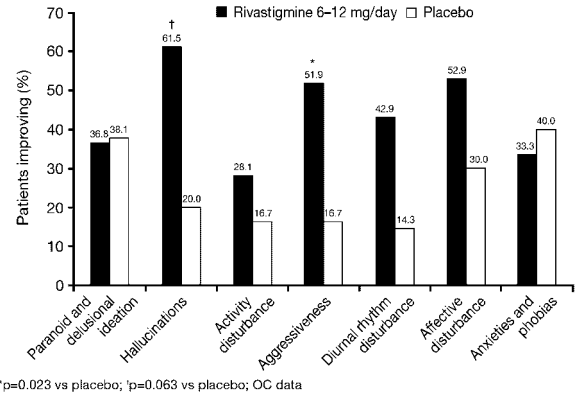

Figure 2. Percentage of subjects with BEHAVE-AD symptoms at baseline experiencing improvement

SAFETY AND TOLERABILITY

Adverse events

Rivastigmine was relatively well tolerated. Gastrointestinal (GI) events, including nausea, vomiting and anorexia were the most frequent AEs (48.4% *vs* 9.1%; 30.6% *vs* 5.5%; 17.7% *vs* 0%, on rivastigmine *vs* placebo, respectively). Other AEs observed with a frequency of at least 10% were dizziness and headache. Agitation was less frequent in subjects treated with rivastigmine than in those receiving placebo (12.9% *vs* 20.0%, respectively). The frequency and type of AEs observed were similar in the moderately severe patients compared with patients with mild dementia (Corey-Bloom *et al.*, 1998; Schneider *et al.*, 1998; Rösler *et al.*, 1999).

Discontinuations

In total, 61.3% of subjects in the rivastigmine group completed the original studies, compared with 67.3% of subjects taking placebo. The most common reason for discontinuing in the rivastigmine and placebo groups was the occurrence of AEs (25.8% *vs* 12.7%, respectively). When the RR of dropping out due specifically to AEs was calculated for rivastigmine *vs* placebo, the risk was lower in these moderately severe subjects (2.0 [95% CI: 0.9–4.6]), compared with subjects with mild dementia (3.6 [95% CI: 2.4–5.4], in subjects with MMSE scores between 22 and 26), indicating that the RR of dropping out due to AEs is related to the level of baseline cognitive impairment.

DISCUSSION

This retrospective analysis of data pooled from three large placebo-controlled phase III studies suggests that rivastigmine is clinically effective in subjects with more severe AD. Although these conclusions are based on small numbers, it should be emphasised that three independent studies contributed similar numbers of subjects and that, furthermore, the findings were highly consistent across the three studies. Treatment with rivastigmine 6–12 mg/day produced benefits across cognitive performance, ADLs, and behavioural symptoms, compared with placebo. For example, 46% of rivastigmine-treated subjects either improved or showed no deterioration on ADAS-Cog, compared with 9% of subjects on placebo (OC population; $p < 0.001$). Subjects also showed stabilisation of cognitive function on the MMSE scale. In addition, according to the PDS six-item score subjects treated with rivastigmine showed less decline on ADLs compared with placebo subjects (1.6 *vs* 6.5 points, respectively; OC population; $p = 0.061$). According to the BEHAVE-AD scale, following 6 months of rivastigmine treatment subjects showed a significant improvement in aggressiveness compared with placebo-treated subjects (OC population; $p = 0.023$).

A recent meta-analysis (Trinh *et al.*, 2003) confirmed the benefits of ChE inhibitors in treating the behavioural and functional symptoms of mild to moderate AD, but described their effects as 'modest'. The findings reported in this paper contribute to growing evidence that patients with more severe AD can also derive clinical benefit from treatment with ChE inhibitors, and show a strong response to treatment. Due to the design of these earlier clinical trials, whereby subjects with baseline MMSE scores <10 were excluded, the benefit of rivastigmine treatment in severe dementia was not documented. However, more recent studies have suggested that a benefit does exist. For example, open-label studies in the nursing home setting examining the effects of rivastigmine in moderate to severe AD patients have demonstrated positive effects on cognitive function and behavioural symptoms (Cummings *et al.*, 2000; Bullock *et al.*, 2001). One placebo-controlled 24-week study in subjects suffering from moderate to severe AD showed a significant benefit of donepezil in the cognitive, functional and behavioural domains (Feldman *et al.*, 2001). These data are supported by the results of a placebo-controlled study in patients with Lewy body dementia, where rivastigmine-treated patients showed improved cognitive function (particularly in attentional deficits), and were significantly less apathetic and anxious, with fewer hallucinations than controls (McKeith *et al.*, 2000). Significant improvements were also seen on the Neuropsychiatric Inventory 10- and 4-item total scores, compared with placebo

(McKeith *et al.*, 2000). In the present study, treatment with rivastigmine improved behavioural symptoms in a large proportion of subjects, which reached statistical significance versus placebo in the BEHAVE-AD item 'aggressiveness'.

One possible explanation for the significant response seen with rivastigmine treatment in more severe AD subjects could relate to the ability of this drug to inhibit BuChE in addition to AChE. This may be of interest within the context of severe disease because studies have indicated that AChE activity decreases as the disease develops, while BuChE activity remains unchanged or increases (Perry *et al.*, 1978; Arendt *et al.*, 1992). Direct measurements of BuChE activity show the most substantial increase in brain areas with more advanced AD pathology (>100 Aβ deposits per mm^3 of brain) (Arendt *et al.*, 1992). Therefore, inhibition of both enzymes by rivastigmine should further preserve ACh levels and may translate into greater and more sustained clinical efficacy in severe disease. In addition, a larger cholinergic deficit exists in severe AD compared with less severe stages of the disease (Davis *et al.*, 1999), which suggests that patients with severe dementia may have a greater potential for improvement with ChE inhibitor therapy than patients with earlier stage disease.

Treatment with rivastigmine was relatively well tolerated in this group of subjects, the most common AEs being cholinergic and GI in nature (e.g. nausea and vomiting). The occurrence of these AEs in the rivastigmine group was similar to that generally reported in other studies, and probably reflects the dose titration used in the early clinical trial protocols. Despite the fast dose titration schedule, the overall proportion of discontinuations due to AEs in the rivastigmine group was still relatively low (25.8%). Since the completion of these trials, experience with rivastigmine (and other ChE inhibitors) in clinical practice has shown that the occurrence of nausea and vomiting can be reduced by using a slow, flexible dose escalation schedule, with a minimum 4-week interval between dose increases (Inglis, 2002). Agitation was less frequent in subjects treated with rivastigmine than in those receiving placebo, suggesting a beneficial effect of rivastigmine on this behavioural symptom of severe AD. Interestingly, the RR of dropping out of the study due to AEs was lower in subjects with more severe dementia compared with mild dementia. We acknowledge that patients with more severe dementia may have increased difficulty reporting adverse events, but also note that the incidence and severity of AEs were similar in subjects with moderately severe dementia and in subjects with mild dementia (Corey-Bloom *et al.*, 1998; Schneider *et al.*, 1998; Rösler *et al.*, 1999).

In conclusion, the results of this analysis, coupled with data from open-label studies in subjects with comparable disease severity, indicate that subjects with more severe AD respond strongly to treatment with the dual ChE inhibitor, rivastigmine. While this is a retrospective subgroup analysis performed on a relatively small number of subjects from a larger data set with all the inherent limitations, the data suggest that the benefits are observed across the domains of ADL, behaviour and cognitive performance. Provision of ChE inhibitors to this group of AD subjects should be actively considered.

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