Rivastigmine monotherapy and combination therapy with memantine in patients with moderately severe Alzheimer’s disease who failed to benefit from previous cholinesterase inhibitor treatment

T. DANTOINE,¹ S. AURIACOMBE,² M. SARAZIN,³ H. BECKER,⁴ J-J PERE,⁵ I. BOURDEIX⁵

Département de Gérontologie Clinique,¹ CHU Limoges, Service de Neurologie;² Hôpital Pellegrin Tripode, Bordeaux; Hôpital de Jour Psycho-gériatrique,³ CHU Bretonneau, Paris; Hôpital Pierre Nouveau,¹ Canne, Novartis Pharma SAS,⁵ Rueil-Malmaison, France

SUMMARY

We investigated the efficacy and safety of rivastigmine alone and combined with memantine in Alzheimer’s disease patients previously failing on donepezil or galantamine. This was a prospective, open-label, multicentre study. After stopping donepezil or galantamine, patients received rivastigmine 3–12 mg/day for 16 weeks. Non-responders to rivastigmine monotherapy at week 16 received memantine 5–20 mg/day plus rivastigmine for 12 weeks. The primary efficacy parameter was response (Mini-Mental State Examination equal or better than at week 16) to dual therapy at week 28. Secondary criteria were changes on cognitive and behavioural scales.

Two hundred and two patients were included. Ninety-three (46.3%) patients responded to rivastigmine monotherapy. Of 86 patients receiving additional memantine for another 12 weeks, 67 (77.9%) responded. Combination therapy caused no apparent safety concerns.

When patients fail on donepezil or galantamine, switching to rivastigmine may improve cognition and behaviour. Should they continue to deteriorate, the addition of memantine may be beneficial.

Keywords: Cognitive decline; Alzheimer’s disease; rivastigmine; memantine; anticholinesterase drugs switch

INTRODUCTION

Alzheimer’s disease (AD) is characterised by progressive decline in neurocognitive functioning. Currently, two classes of drugs are recommended for the symptomatic treatment of AD, each targeting a different neurochemical component thought to underlie the condition. The rationale for the development of cholinesterase inhibitors was the now well-known ‘cholinergic hypothesis’ (1) that the progressive loss of cholinergic neurones seen in the AD brain, and the resulting decline in levels of the neurotransmitter, acetylcholine, correlates with cognitive decline. In addition, it has been shown that, in AD, continuous stimulation of N-methyl-D-aspartate (NMDA) receptors by glutamate triggers a cascade of biochemical events that damage and kill surrounding neurones.

This formed the rationale for developing NMDA receptor antagonists for the treatment of AD (2).

The cholinesterase inhibitors are widely recommended for the treatment of mild to moderate AD (3,4). Although all approved cholinesterase inhibitors enhance cholinergic function in the brain by inhibiting the enzyme(s) that degrades acetylcholine, individual agents differ with regard to their pharmacological profiles (5). The three most widely used cholinesterase inhibitors are rivastigmine (Exelon®), a sustained inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), and the AChE-selective inhibitors, donepezil (Aricept®) and galantamine (Reminyl®, Razadyne®). The clinical significance of additional BuChE inhibition is still elucidated, but it has been proposed that pharmacological differences may differentiate the cholinesterase inhibitors with respect to clinical efficacy and safety (5).

Such differences may underlie clinical findings that patients who fail on one agent may benefit from another, leading to the suggestion that patients not responding to one cholinesterase inhibitor should be switched to another agent in the same class (6–9).

In 2004, the first NMDA receptor antagonist was approved for the treatment of moderate to severe AD. Memantine (Ebixa®) is believed to replace the magnesium ion in a
‘pathologically activated’ receptor, blocking the ion channel and rendering it inactive (10). In this way, memantine may protect the neuronal system from pathological activation while preserving physiological activation. NMDA receptor antagonists are unlikely to replace the cholinesterase inhibitors as first-choice therapy in AD, but because the two classes of drug are believed to work on different mechanisms that may result in symptoms of AD, it seems reasonable to hypothesise that additive effects may be achieved from combination therapy. A randomised controlled trial of memantine treatment in AD patients already receiving a cholinesterase inhibitor appeared to support this hypothesis (11).

Nevertheless, memantine’s place in the treatment algorithm for AD remains unclear. No current treatment can stop the progression of AD, although decline in patients receiving cholinesterase inhibitors can be significantly slower and later than expected if patients were left untreated (12). Therefore, as cholinesterase inhibitors are recommended for mild to moderate AD and memantine for moderate to severe AD and moreover as the cholinesterase inhibitors differ pharmacologically and some patients fail on their original cholinesterase inhibitor treatment, it might be possible to develop an algorithm that reflects the best use of these drugs in appropriate patients. In the current study, we aimed to determine the safety and efficacy of memantine when added to rivastigmine treatment in patients with AD who were receiving rivastigmine after previously failing to benefit from donepezil or galantamine.

**METHODS**

**Patients**

Study subjects were male and female outpatients with caregivers. Patients had to be at least 50 years of age, with probable AD according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria (13). They had baseline Mini-Mental State Examination (MMSE) scores of <18, or Global Deterioration Scale (GDS) scores of >4, indicating moderate to severe dementia (14,15).

All patients included in the study had been treated with either donepezil (5–10 mg/day) or galantamine (16–24 mg/day) for at least 6 months prior to study entry. In the investigators’ clinical judgement, the patients had not stabilised on treatment with donepezil or galantamine as evidenced by two criteria: (i) a decline in cognitive functioning while on donepezil or galantamine treatment (a loss of ≥2 points on the MMSE within the previous 6 months or 3 points during the previous year) and (ii) either a clinical decline, as determined by the investigator, in activities of daily living, behaviour or global functioning, or caregiver dissatisfaction with patient response (lack of therapeutic effect/benefit).

Concomitant medications were permitted, although psychotropic drugs (neuroleptics, antidepressants, sedatives, hypnotics and antiepileptics) had to be stable for at least 1 month before inclusion and given at the lowest possible dose. The use of concomitant tricyclic agents was forbidden. Patients with evidence of severe or unstable physical illness were excluded from the study. This included acute and severe asthmatic conditions, severe or unstable cardiovascular disorders, active peptic ulcer disease, known hypersensitivity to cholinesterase inhibitors or memantine, clinically significant laboratory abnormalities or any medical condition that would prohibit the patient from completing the clinical trial.

**Study Design**

This was a prospective, multicentre, open-label study that comprised two phases. Following screening and baseline assessments, eligible patients were switched from either donepezil or galantamine to rivastigmine and entered Phase 1, the 16-week rivastigmine treatment phase. The minimum and maximum permitted times between the last dose of donepezil or galantamine and initiation of rivastigmine were 1 day (the day after the last dose of donepezil or galantamine) and 7 days, respectively. Patients began Phase 1 with capsules of rivastigmine 1.5 mg bid (3 mg/day, taken with food). The dose of rivastigmine was escalated in 1.5 mg bid steps at 4-week intervals to the highest tolerated dose up to 6 mg bid (12 mg/day). The overall dosing strategy was to treat patients at the highest doses that were individually well tolerated, but dose adjustments were permitted and left to the investigators’ judgement. Patients unable to tolerate the minimum dose of rivastigmine (1.5 mg bid) were discontinued.

Patients who had stabilised, as defined by an MMSE score that was equal to or better than baseline, on rivastigmine at the end of Phase 1 were considered to have completed the study. The further treatment of these patients rested upon the investigators’ judgement. The same treatment strategy could be continued, or it could be adjusted or modified at any time in accordance with current medical practice. Patients who were not sufficiently stabilised, as defined by an MMSE score that was worse than baseline, on rivastigmine alone at the end of Phase 1 received memantine in addition to rivastigmine for a further 12 weeks in Phase 2. Patients began Phase 2 with the rivastigmine dose at which they had finished Phase 1, plus memantine 5 mg/day (half a tablet, with breakfast) during the first week. The dose of memantine was increased in 5 mg/day steps, at weekly intervals, so that in the second week of Phase 2, patients received half a tablet twice a day (10 mg/day), in the third week one tablet in the morning and half a tablet in the afternoon (15 mg/day) and in the fourth week patients received one tablet twice a day (20 mg/day). Patients unable to tolerate the minimum dose of memantine (5 mg/day) were discontinued.

The study was conducted in accordance with ethical standards of the responsible committees on human experimentation.
and with the Helsinki Declaration. The study protocol was approved by the Limoges Institutional Review Board. Written informed consent was obtained for all patients at the screening visit.

Outcome Measures

The primary efficacy measure was a proportion of responders on the MMSE (14) at the end of Phase 2. The responder was defined as the patient with an MMSE score at week 28 that was equal to or better than the end of Phase 1 (increase of ≥0 points). Secondary efficacy criteria were changes at week 28 compared with the end of Phase 1, on the MMSE (14), mini-Zarit Inventory (Burden of Caregiver) (16), Neuropsychiatric Inventory (NPI) (17), Ten-point Clock-drawing test (18) and Delis–Kaplan Executive Function System (D-KEFS) verbal fluency test (19). At the end of Phase 1, the same efficacy measures were used, but responder rates or scores at week 16 (the end of Phase 1) were compared with those at baseline. In addition, Clinical General Impression of Change (CGI-C) (20) responses were recorded at weeks 16 and 28. When possible, patients who discontinued treatment prematurely had their week 16 evaluations or their week 28 evaluations performed at the time of discontinuation.

Safety evaluations include vital signs, adverse events, prior and concomitant medications and therapies and a physical examination. Tolerability was assessed by the proportion of patients able to reach and maintain target dose levels at the end of the scheduled titration periods.

Statistical Analyses

A sample size of 450 patients was initially calculated on the assumption that about 50% of patients would enter Phase 2 (7), and about 15% of patients were expected to respond to dual therapy. However, because of difficulties with recruitment (due to common use of initial dual therapy for patients with MMSE scores lower than 15), the sample size was revised to 200.

Patients who had at least one dose of study medication and had at least one safety evaluation postbaseline comprised the safety population. Efficacy analyses were based on an intent-to-treat (ITT) population, defined as all randomised patients who received study medication. In addition, for the primary outcome measure (MMSE responder analyses), supportive analyses comprised a per-protocol (PP) population of ITT patients excluding major protocol deviations, and an observed case (OC) population including all ITT patients who had evaluations on treatment at designated assessment times. The paired Wilcoxon Signed Rank Test was used to analyse changes from baseline on the MMSE, NPI, Ten-point Clock-drawing Test, the D-KEFS verbal fluency test and the Zarit inventory.

RESULTS

Patients

The study began in November 2003, and the last patient visit took place in February 2005. Two hundred and seven patients from 51 centres were selected, of whom 202 met inclusion criteria for study participation, 178 completed Phase 1 and 82 completed Phase 2.

Baseline characteristics of the total population and those who subsequently entered Phase 2 did not appear to differ markedly (Table 1). When subgroups of patients previously receiving donepezil or galantamine were looked at separately, mean ages of patients previously treated with donepezil and galantamine were 78.0 and 77.7 years, respectively. There was a tendency for a shorter duration of previous treatment in the subgroup previously receiving galantamine (Table 1). In addition, more patients previously treated with galantamine had mild impairment (GDS score of 4) at baseline compared with patients previously treated with donepezil (11.9 vs. 1.7%). However, prevalences of severe impairment (GDS score of 6) were similar in the two subgroups (23.8 and 23.3%, respectively). The median time between stopping previous treatment with donepezil or galantamine and initiating rivastigmine treatment was 2.0 days.

The majority of patients (86.6%) had concurrent medical conditions at baseline, before the start of study medication. Most common were vascular disorders (48.8%, most commonly hypertension), metabolism and nutrition disorders (28.4%, most commonly hypercholesterolaemia and diabetes) and psychiatric disorders (21.9%, most commonly depression). Concomitant treatments were being taken by 75.1% of patients at baseline. These were most frequently psychotropic agents (antipsychotics, anxiolytics, hypnotics and sedatives; taken by 26.4% of patients) and psychoanaleptics (antidepressants, psychostimulants, nootropics and gingko biloba; taken by 26.9% of patients).

Efficacy

At the end of Phase 1, 93 (46.3%) patients overall had improved (28.4%) or stabilised (17.9%) on rivastigmine treatment alone, according to their MMSE scores. Findings in the PP and OC populations were similar and supportive. Responder rates were similar in patients previously receiving donepezil (46.6%) and galantamine (46.4%) at the end of Phase 1.

Eighty-six patients entered Phase 2 and received memantine in addition to rivastigmine. During this phase, 67 (77.9%) patients improved (51.2%) or stabilised (26.7%) on dual therapy, according to their MMSE scores (Figure 1). Significantly more patients switching from galantamine responded to treatment compared with those switching from donepezil (84.2 vs. 72.3% improved or stabilised;...
In the overall population, the CGI-C response data were consistent with findings on the MMSE. CGI-G data showed that at the end of Phase 1, 51.3% of all patients had improved or showed no change (Figure 2). Of the patients who completed the study at the end of Phase 1 (either having satisfied the criteria of stabilising on rivastigmine treatment during Phase 1 or discontinuing prematurely during that phase), 76.5% of patients showed no change or improvements on the CGI-C (Figure 2). In contrast, of the 86 patients not stabilised on rivastigmine therapy according to their MMSE scores at the end of Phase 1, 82.6% were worse than baseline on the CGI-C. When these patients received memantine in addition to rivastigmine, 81.4% showed improvement or no change during Phase 2.

Among patients who completed the study at the end of Phase 1 (which included patients who had discontinued treatment, as well as those who stabilised under rivastigmine alone), significant improvements on the MMSE and NPI total scores were observed at the end of Phase 1 (Table 2). Mean scores on the Ten-point Clock-Drawing Test and the D-KEFS verbal fluency test were maintained at baseline levels, suggesting that rivastigmine alone may have prevented the worsening of this measure of executive dysfunction in these patients. There was also no change in caregiver satisfaction as assessed using the Mini-Zarit interview.

Patients who entered Phase 2 of the study showed significant declines on their mean MMSE, D-KEFS verbal fluency Test and Mini-Zarit scores at the end of Phase 1 (Table 2). The addition of memantine in Phase 2 resulted in a significant improvement on the MMSE that brought this group’s mean score half way back to baseline levels. No other scores were statistically significantly improved following the addition of memantine.

Safety and Tolerability

At the end of Phase 1, the mean dose of rivastigmine received by all patients in the Safety population was 9.2 mg/day. Within this population, the 86 patients who subsequently

---

Table 1 Characteristics of the trial population at baseline (safety population)

|                          | Phase 1 (n = 201) | Phase 2 (n = 86) |
|--------------------------|-------------------|-----------------|
| Mean (SD) age, years     | 77.9 (6.5)        | 77.4 (7.5)      |
| Gender, n (%) men        | 82 (40.8)         | 36 (41.9)       |
| Mean (SD) duration of AD, months | 27.4 (17.3) | 29.2 (17.0)   |
| Mean (SD) baseline MMSE score | 15.5 (3.4) | 15.3 (3.1)    |
| Baseline GDS rating, n (%) |                  |                 |
| 4 – Mild impairment      | 12 (6.0)          | 2 (2.3)         |
| 5 – Moderately severe impairment | 142 (70.6) | 56 (65.1)     |
| 6 – Severe impairment    | 47 (23.4)         | 28 (32.6)       |
| Prior medication, n (%)* |                  |                 |
| Donepezil 5–10 mg/day   | 116 (57.7)        | 47 (54.7)       |
| Galantamine 8–24 mg/day  | 84 (41.8)         | 38 (44.2)       |
| Mean (SD) duration of prior medication, months |         |                 |
| Donepezil 5–10 mg/day   | 26.7 (17.9)       | 26.5 (16.8)     |
| Galantamine 8–24 mg/day  | 17.1 (9.5)        | 19.8 (9.8)      |
| Total                   | 22.6 (15.6)       | 23.5 (14.4)     |
| Mean (SD) previous total decline on MMSE throughout duration of prior medication |         |                 |
| Donepezil 5–10 mg/day   | −5.4 (2.8)        | −5.8 (2.7)      |
| Galantamine 8–24 mg/day  | −5.1 (2.7)        | −5.1 (2.4)      |
| Total                   | −5.3 (2.8)        | −5.5 (2.6)      |
| Mean (SD) previous annual decline on MMSE estimated for prior medication period |         |                 |
| Donepezil 5–10 mg/day   | −3.4 (2.9)        | −3.5 (2.5)      |
| Galantamine 8–24 mg/day  | −5.2 (6.7)        | −4.1 (3.6)      |
| Total                   | −4.2 (4.9)        | −3.8 (3.0)      |
| Reasons for previous treatment failure, n (%) |         |                 |
| Caregiver dissatisfaction| 178 (88.6)        | 81 (94.2)       |
| Clinical decline†       | 200 (99.5)        | 86 (100)        |

AD, Alzheimer’s disease; GDS, Global Deterioration Scale; MMSE, Mini-Mental State Examination. Baseline (Week 0) data for patients entering Phase 2 are shown separately, although these are included in the 201 patients entering Phase 1. *One additional patient previously failed on both donepezil and galantamine and is not included here. †As determined by the investigator, in activities of daily living, behaviour or global functioning.
Figure 1 Mini-Mental State Examination (MMSE) responders at the end of Phase 2 (showing ≥0-point improvement compared with scores at the end of Phase 1; intent-to-treat (ITT) population). *One additional patient previously failed on both donepezil and galantamine and is not included here.

Figure 2 Clinical General Impression of Change (CGI-C) responders at the ends of Phase 1 and 2 (intent-to-treat population). Percentages may not total 100% because of some patients not providing CGI-C data.
entered Phase 2 were receiving a mean dose of 9.9 mg/day at the end of Phase 1. By the end of Phase 2, the mean dose of rivastigmine received by these patients was 10.3 mg/day. There was a tendency for patients entering Phase 2 to take higher doses of rivastigmine, and more of these patients reached higher target doses (Table 3). At the end of Phase 2, the mean dose of memantine was 19.0 mg/day (Table 3).

Table 2  Mean score changes on the MMSE, NPI, Ten-point Clock-drawing Test, D-KEFS verbal fluency test and the mini-Zarit Inventory at the end of Phase 1 (compared with baseline scores) and Phase 2 (compared with scores at the end of Phase 1) (ITT population)

| Outcome measure          | Total (n = 201) | Patients completing the study at the end of Phase 1† (n = 115) | Patients continuing in the study until the end of Phase 2 (n = 86) |
|--------------------------|----------------|---------------------------------------------------------------|---------------------------------------------------------------|
|                          | Mean (SD) scores | Mean (SD) change | Mean (SD) scores | Mean (SD) change | Mean (SD) scores | Mean (SD) change |
| MMSE                     |                |                  |                  |                  |                  |                  |
| Baseline                 | 15.5 (3.4)     | –                 | 15.7 (3.6)       | –                 | 15.3 (3.1)       | –                 |
| End Phase 1              | 15.3 (4.3)     | −0.2 (2.5)       | 17.0 (4.4)       | 1.3 (2.2)**       | 13.2 (3.2)       | −2.1 (1.4)**      |
| End Phase 2              | –              | –                 | –                |                  | 14.3 (4.1)       | 1.2 (2.5)**       |
| NPI                      |                |                  |                  |                  |                  |                  |
| Baseline                 | 19.0 (16.9)    | –                 | 19.8 (16.6)      | –                 | 17.8 (17.3)      | –                 |
| End Phase 1              | 16.9 (15.1)    | −1.4 (9.2)       | 16.8 (14.9)      | −2.1 (9.7)*       | 17.1 (15.4)      | −0.4 (8.4)        |
| End Phase 2              | –              | –                 | –                |                  | 15.4 (14.5)      | −0.8 (7.2)        |
| Ten-point Clock-drawing Test
| Baseline                 | 2.6 (3.2)      | –                 | 3.1 (3.5)        | –                 | 2.0 (2.7)        | –                 |
| End Phase 1              | 2.6 (3.4)      | −0.1 (2.7)       | 3.4 (3.7)        | 0.0 (2.7)         | 1.6 (2.6)        | −0.3 (2.7)        |
| End Phase 2              | –              | –                 | –                |                  | 2.2 (2.8)        | 0.5 (2.2)         |
| D-KEFS verbal fluency test
| Baseline                 | 7.3 (3.8)      | –                 | 7.9 (4.0)        | –                 | 6.4 (3.3)        | –                 |
| End Phase 1              | 7.1 (4.2)      | −0.3 (2.7)       | 8.2 (4.5)        | 0.0 (3.2)         | 5.8 (3.5)        | −0.7 (2.0)*       |
| End Phase 2              | –              | –                 | –                |                  | 6.2 (3.6)        | 0.5 (2.7)         |
| Mini-Zarit               |                |                  |                  |                  |                  |                  |
| Baseline                 | 3.8 (1.6)      | –                 | 3.6 (1.6)        | –                 | 3.9 (1.6)        | –                 |
| End Phase 1              | 3.8 (1.7)      | 0.1 (1.1)        | 3.6 (1.6)        | −0.1 (1.1)        | 4.2 (1.6)        | 0.3 (1.0)**       |
| End Phase 2              | –              | –                 | –                |                  | 4.1 (1.6)        | −0.1 (0.6)        |

D-KEFS, Delis–Kaplan Executive Function System; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory. *p < 0.05 or **p < 0.001 vs. baseline or end Phase 1 score; †Including patients who discontinued prematurely during Phase 1.

Table 3  Study medication dosing and exposure to treatment (safety population)

| Rivastigmine               | Patients entering Phase 1 (n = 201) | Patients entering Phase 2 (n = 86) |
|----------------------------|-------------------------------------|-----------------------------------|
| Mean (SD) rivastigmine dose (mg/day) at 16 weeks (end of Phase 1) | 9.2 (2.8) | 9.9 (2.6) |
| Mean (SD) rivastigmine dose (mg/day) at 28 weeks (end of Phase 2) | – | 10.3 (2.6) |
| Patients reaching rivastigmine doses at end of study*, n (%) |                  |                  |
| ≤3 mg/day | 9 (4.5) | 1 (1.2) |
| 3 to ≤6 mg/day | 48 (23.9) | 17 (19.8) |
| >6 to ≤9 mg/day | 50 (24.9) | 12 (14.0) |
| >9–12 mg/day | 94 (46.8) | 56 (65.1) |
| Mean (SD) treatment duration, days | Phase 1 | 109.3 (23.4) | 113.9 (11.2) |
|                       | Phase 2 | – | 81.9 (17.4) |
| Memantine              | Patients entering Phase 1 (n = 201) | Patients entering Phase 2 (n = 86) |
| Mean (SD) memantine dose (mg/day) at 28 weeks (end of Phase 2) | – | 19.0 (3.3) |
| Mean (SD) treatment duration, days | – | 81.9 (17.4) |

*End of study was week 16 for patients stabilising on rivastigmine during Phase 1 and week 28 for patients entering Phase 2 or at early discontinuation.
Eighty-two (40.8%) patients who entered Phase 1 (and who may have continued into Phase 2) reported at least one adverse event, 65 (32.3%) of which were suspected to be related to rivastigmine treatment. The most common adverse events were nausea and vomiting (Table 4). During Phase 2, five (5.8%) patients reported at least one new adverse event, one (1.2%) of which was suspected to be related to study medication. No clinically significant changes in heart rate or diastolic or systolic blood pressure were apparent. There was a slight weight loss during Phase 1 (mean 0.3 kg loss, \( n = 201 \)) and a slight regaining of weight during Phase 2 (mean 0.2 kg gain, \( n = 86 \)).

Serious adverse events were reported by 14 (7.0%) and 1 (1.2%) patient during Phases 1 and 2, respectively. Most of these [11 (5.5%) and 1 (1.2%), respectively] were not suspected to be related to study medication. Of patients entering Phase 1, 15 (7.5%) discontinued the study prematurely because of adverse events, including two deaths and one discontinuation in Phase 2 because of an event reported during Phase 1, compared with 1 (1.2%) in Phase 2. The causes of the two deaths were probable myocardial infarction and cardiac arrest. Both deaths were considered by the investigators to be unrelated to study medication.

**DISCUSSION**

This study supports previous findings that many patients failing to respond to an AChE-selective inhibitor may benefit across a range of symptom domains from being switched to rivastigmine. The 46% response rate at the end of Phase 1 was consistent with previous findings that up to 50% of patients unsuccessfully treated with donepezil appear to benefit from being switched to rivastigmine (9). Using the same criterion of response according to stabilised or improved MMSE scores, Auriacombe et al. (7) previously demonstrated similar response rates of about 50% in patients previously failing on donepezil. Switching to rivastigmine was equally effective irrespective of which AchE inhibitor had been used previously (donepezil or galantamine). Furthermore, the findings support the hypothesis that patients unable to respond adequately to any cholinesterase inhibitor may obtain cognitive benefits from concomitant therapy with an NMDA receptor antagonist. These are important findings that may help to define the role of these agents in the treatment of AD.

The baseline characteristics of the current population with moderately severe AD (mean MMSE score of 15.5) did not reveal any clear predictors of response to rivastigmine or the need for concomitant memantine. Patients who failed to respond to rivastigmine at the end of Phase 1 were of a similar age and gender to the overall population, and they had showed similar declines on previous therapy with donepezil or galantamine. The main apparent difference was that patients who failed to respond to rivastigmine had a tendency towards more advanced stages of AD and slightly longer disease duration at baseline. Pathological factors that might underlie differential responses to cholinesterase inhibitors and NMDA receptor antagonists could be an interesting area for further study.

Response to rivastigmine monotherapy did not seem to be explained by doses received during Phase 1. At the end of Phase 1, the mean dose of rivastigmine reached by all patients was 9.2 mg/day while that in the subgroup that later entered Phase 2 was 9.9 mg/day. This suggests that failure to improve or stabilise on the MMSE was not because of an inability to reach adequate doses of the drug, rather these patients managed to reach higher doses but were still not responding to cholinesterase inhibitor therapy.

This study was limited by its open-label nature and by the use of real-world entry criteria that included subjective measures such as investigator opinion or caregiver dissatisfaction. It seems feasible that caregivers with overly optimistic expectations of any treatment were more likely to report treatment failure, and this may have affected the findings. Nevertheless, this study design captured a reasonable reflection of real-world clinical practice, and findings on the MMSE appeared to be validated by the GDS results. Statistical significance was reached on a number of outcome measures despite the sample size being smaller (and thus statistical power lower) than originally intended.

The favourable tolerability and safety profiles of rivastigmine and memantine were demonstrated by the relatively high mean doses reached and the relatively low discontinuation rates because of adverse events in both the phases. Compared with regulatory studies, relatively few patients discontinued because of adverse events during Phase 1. In particular, nausea and vomiting were reported much less frequently than in pivotal studies of rivastigmine (21–23). The cholinergic gastrointestinal effects of all cholinesterase inhibitors are centrally mediated, caused by rapid elevations of acetylcholine in the area postrema, the putative ‘vomiting centre’ in the brain. However, all patients in the current study had been receiving prior cholinesterase inhibitor therapy;

**Table 4** Number (%) of patients reporting the most common* adverse events (safety population)

| Adverse event | Phase 1 (n = 201) | Phase 2 (n = 86) |
|---------------|------------------|-----------------|
| Nausea        | 30 (14.9)        | 1 (1.2)         |
| Vomiting      | 9 (4.5)          | 1 (1.2)         |
| Agitation     | 8 (4.0)          | 0 (0.0)         |
| Malaise       | 8 (4.0)          | 0 (0.0)         |
| Anorexia      | 7 (3.5)          | 0 (0.0)         |
| Diarrhoea     | 7 (3.5)          | 0 (0.0)         |
| Dizziness     | 7 (3.5)          | 0 (0.0)         |
| Asthenia      | 5 (2.5)          | 0 (0.0)         |

*Adverse events reported by at least 2% of patients in either phase are listed.
therefore, their brains may have become desensitised to the effects of increased levels of acetylcholine. Moreover, during Phase 2, adverse events were very rare. It has been shown previously that once rivastigmine has been titrated to maximum tolerated doses, as it was during Phase 1, it is well tolerated during the maintenance phase of treatment (24). No additional adverse events or safety concerns appeared to be caused by the addition of memantine. It is not thought that the action of rivastigmine was reduced by co-administration of memantine, because it has been shown previously that the inhibitory actions of rivastigmine are unaffected by co-administration of memantine (25).

The cost-effectiveness of dual therapy was not assessed in the current study. However, the use of rivastigmine alone has previously been shown to result in cost savings for the community (26), and it seems feasible to suggest that an algorithm that proposes the appropriate use of additional therapy only when needed, or when most likely to be beneficial, should be a cost-favourable strategy. The pharmacoeconomics of dual rivastigmine and memantine therapy would be an interesting subject of further study.

In conclusion, if a patient with AD is not responding to treatment with an AChE-selective inhibitor, the physician may consider switching them to the dual inhibitor, rivastigmine. This switch may result in improvements in cognition and behaviour and stabilisation of executive function. Should the patient continue to deteriorate under rivastigmine at any time, his or her cognitive performance may improve following the addition of concomitant memantine therapy. The addition of memantine to rivastigmine appears to cause no significant additional safety or tolerability concerns. While this algorithm requires validation in further studies, it may provide an effective treatment pathway for AD.

ACKNOWLEDGEMENTS

This study was supported by Novartis Pharma SAS, Rueil-Malmaison, France.

REFERENCES

1 Davies KL, Maloney AJ. Selective loss of central cholinergic neurons in Alzheimer’s disease. *Lancet* 1976; 2: 1403.
2 Danysz W, Parsons CG, Möbius H-J, Stöfferl A, Quack G. Neuroprotective and symptomatical action of memantine relevant for Alzheimer’s disease – a unified glutamatergic hypothesis on the mechanism of action. *Neuroreport* 2000; 2: 85–97.
3 Doody RS, Stevens JC, Beck C et al. Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001; 56: 1154–66.
4 Clegg A, Bryant J, Nicholson T et al. Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer’s disease: a rapid and systematic review. *Health Technol Assess* 2001; 5: 1–137.
5 Poirier J. Evidence that the clinical effects of cholinesterase inhibitors are related to potency and targeting of action. *Int J Clin Pract Suppl* 2002; 127: 6–19.
6 Ferris SH. Switching previous therapies for Alzheimer’s disease to galantamine. *Clin Ther* 2001; 23 (Suppl. A): A3–7.
7 Auriacombe S, Pere JJ, Loria-Kanza Y, Vellas B. Efficacy and safety of rivastigmine in patients with Alzheimer’s disease who failed to benefit from treatment with donepezil. *Curr Med Res Opin* 2002; 18: 129–38.
8 Emre M. Switching cholinesterase inhibitors in patients with Alzheimer’s disease. *Int J Clin Pract Suppl* 2002; 127: 64–72.
9 Gauthier S, Emre M, Farlow MR, Bullock R, Grossberg GT, Potkin SG. Strategies for continued successful treatment of Alzheimer’s disease: switching cholinesterase inhibitors. *Curr Med Res Opin* 2003; 19: 707–14.
10 Parsons CG, Danysz W, Quack G. Memantine and the aminooctyl-cyclohexane MRZ 2/579 are moderate affinity uncompetitive NMDA receptor antagonists – *in vitro* characteristics. *Amino Acids* 2000; 19: 157–66.
11 Tariot PN, Farlow MR, Grossberg GT et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA* 2004; 291: 317–24.
12 Bullock R, Dengiz A. Cognitive performance in patients with Alzheimer’s disease receiving cholinesterase inhibitors for up to 5 years. *Int J Clin Pract* 2005; 59: 817–22.
13 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. Washington, DC: American Psychiatric Association, 1994.
14 Folstein MF, Folstein SE, McHugh PR. ‘Mini-Mental State’: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12: 189–98.
15 Reisberg B, Ferris SH, de Leon MJ, Crook T. The global deterioration scale for assessment of primary degenerative dementia. *Am J Psychiatry* 1982; 139: 1136–9.
16 Revel Da Rocha V, Haritchabalet I, Kervinio C et al. Construction d’une échelle simplifiée pour la détection en médecine générale du fardeau de l’aidant d’une personne, gée dépendante. *L’Année Gérontologique* 2002; 16: 131–7.
17 Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994; 44: 2308–14.
18 Manos PJ, Wu R. The ten point clock test: a quick screen and grading method for cognitive impairment in medical and surgical patients. *Int J Psychiatry Med* 1994; 24: 229–44.
19 Delis DC, Kaplan E, Kramer JH. Delis-Kaplan Executive Function System. Texas: Psychological Corporation, 2001.
20 Guy W. *ECDEU Assessment Manual for Psychopharmacology*. Rockville, MD: U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, 1976; 218–22.
21 Corey-Bloom J, Anand R, Veach J. A randomized trial evaluating the efficacy and safety of ENA 73 (rivastigmine tartrate), a
new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer disease. *Int J Ger Psychopharmacol* 1998; 1: 55–65.

22 Schneider A, Anand R, Farlow M. Systematic review of the efficacy of rivastigmine for patients with Alzheimer disease. *Int J Ger Psychopharmacol* 1998; 1: S26–34.

23 Rösler M, Anand R, Cicin-Sain A et al. Efficacy and safety of rivastigmine in patients with Alzheimer disease: international randomised controlled trial. *BMJ* 1999; 318: 633–8.

24 Bullock R, Touchon J, Bergman H et al. Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer’s disease over a 2-year period. *Curr Med Res Opin* 2005; 21: 1317–27.

25 Enz A, Gentsch C. Co-administration of memantine has no effect on the in vitro or ex vivo determined acetylcholinesterase inhibition of rivastigmine in the rat brain. *Neuropharmacology* 2004; 47: 408–13.

26 Lamb HM, Goa KL. Rivastigmine – a pharmacoeconomic review of its use in Alzheimer’s Disease. *Pharmacoeconomics* 2001; 19: 303–18.

*Paper received September 2005, accepted November 2005*