



The AD2000 study of donepezil for Alzheimer's disease

A summary of results for health care professionals

June 12th 2004

Background

Dementia is common with an estimated 700,000 people affected in the UK alone, of whom about 400,000 have Alzheimer's disease. It is expensive to treat: the Audit Commission estimates the total annual costs of dementia care in the UK to be £6.1 billion (at 1998/99 prices). Cholinesterase inhibitors were developed to increase acetylcholine levels in the brain, which are lowered in Alzheimer's disease. The drugs have been shown to improve scores on cognitive tests and clinical impression of change. As a result, donepezil (Aricept[®]) was licensed in the UK, in March 1997, followed by two other cholinesterase inhibitors, rivastigmine (Exelon[®]) and galantamine (Reminyl[®]). In 2001, the National Institute for Clinical Excellence recommended that the drugs should be made available in the NHS for people with mild to moderate AD, with treatment continuing while there is clinical evidence of response

However, the clinical relevance of the small benefits from cholinesterase inhibitors seen in the licensing trials is questionable. The AD2000 trial was, therefore, set up, with funding from the NHS Executive R&D, to determine whether donepezil and/or aspirin produce clinically, socially and economically worthwhile benefits for typical patients with Alzheimer's disease and, if so, which patients benefit, from what dose, and for how long. To avoid any bias, in assessing outcome, the study was double-blind (i.e. patients, their carers and doctors did not know whether the patient was taking donepezil or placebo). The patient's treatment continued as long as doctor and carer considered it appropriate.

The trial opened to recruitment in October 1998. 566 patients with mild to moderate Alzheimer's disease were randomised, over a period of 3 years, from 22 centres across England and Wales. The mean age of the patients in the trial was 75 years, with a range from 46 to 93 years. A full report of the findings was published in the Lancet of June 26th 2004. The main results are summarised below.

Donepezil produced small but definite improvements in tests of cognitive and functional ability, similar to those seen in previous trials:

- Memory impairment was assessed using the Mini-mental State Examination (MMSE). Over the first two years of treatment, patients taking donepezil scored, on average, 0.8 points better on the 30-point MMSE scale than those taking placebo.
- Patients' ability to perform activities of daily living was assessed using the Bristol Activities of Daily Living Scale (BADLS). Patients taking donepezil scored, on average, 1.0 points better on the 60-point BADLS scale than patients taking placebo over the first 2 years of treatment.

But, there was no significant delay in entry to institutional care or progress of disability, the two primary outcome measures:

- There was no significant delay in entry to institutional care: 42% of patients taking donepezil were in permanent care at three years compared to 44% of patients taking placebo.
- The BADLS was used to specify a second 'progression of disability' primary outcome measure defined by loss of either 2 out of 4 'basic', or 6 out of 11 'instrumental', activities of daily living. These criteria represented an increased level of dependency that would require substantial increases in caregiver time. Taking donepezil did not delay patient's progress to this level of disability. At 3 years 58% of patients taking donepezil, and 59% of patients taking placebo had reached this increased level of disability.

No statistically significant improvement in any other outcome measures:

- Taking donepezil did not affect the frequency or severity of the behavioural and psychological problems associated with dementia. The Neuropsychiatric Inventory (NPI) was used to assess the patient's behavioural and psychological problems. Patients scored 0.3 points better with donepezil than placebo on the 144-point NPI scale.
- The high levels of depression/anxiety symptoms experienced by carers of patients with Alzheimer's disease were not improved by donepezil. The level of depression/anxiety was measured using the General Health Questionnaire (GHQ30). The carer's of patients taking donepezil scored, on average, 0.3 points better on this 30-point scale than carers of patients taking placebo.
- Taking donepezil did not reduce patients' NHS or social service care requirements. Costs of paid care (e.g. hospital stays, GP visits, visiting nurses, social workers but excluding the cost of donepezil) were £2,842 per year for patients taking donepezil and £2,344 per year for patients taking placebo.
- Taking donepezil did not significantly reduce the time unpaid carers, e.g. family, friends and neighbours, spent actively caring for the patient (average of 11 minutes less per day with donepezil), or in supervising the patient (22 minutes less with donepezil).
- There were no significant differences seen between patients taking 5mg or 10mg of donepezil, on any measures assessed in the trial.
- No subgroup of patients could be identified who derived greater or lesser benefit from donepezil. Patient characteristics such as age, genetic make-up, severity of disease, other co-existing illnesses, or measurements of response after 12 weeks of treatment cannot be used to target treatment at patients more likely to derive benefit from donepezil.

Interpretation of these results

Donepezil treatment of Alzheimer's disease does not significantly delay patient's progress to a higher level of disability, or delay entry to institutional care. It does not reduce the costs or burden of caring for patients with Alzheimer's disease, or affect the frequency and severity of behavioural and psychological problems associated with dementia. 10mg donepezil is no better than 5mg donepezil, and it is not possible to target treatment at groups of patients who are more likely to benefit from

donepezil than others. Donepezil does produce small improvements in patient's scores on tests of memory and ability to perform activities of daily living, but these are below predefined minimal clinically important levels. It is unlikely that the changes would lead to a worthwhile improvement in the patient's health related quality of life. Donepezil use is therefore not cost-effective and better medical and non-medical treatments are needed for AD.

Acknowledgements

Our main thanks are to the patients and carers who took part in the AD2000 study without whose help this study would not have been possible. The AD2000 trial would also not have succeeded without the support given to it by the NHS clinicians, nurses, and pharmacists who made up the AD2000 Collaborative Group. We also thank the NHS Executive R&D (West Midlands), who funded the central organisation and the Health Authorities in the West Midlands, East Lancashire, Iechyd Morgannwg, and North Nottingham who funded the drug costs.

AD2000 publication: AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet 2004; 363: 2105-2115.

Further information on the AD2000 trial is available from the AD2000 Study Office, University of Birmingham Clinical Trials Unit, Park Grange, 1 Somerset Rd, Birmingham B15 2RR. Tel: +44 (0) 121 687 2317/2310, fax, +44 (0) 121 687 2313, e-mail: ad2000@bham.ac.uk, web site: www.ad2000.bham.ac.uk