AD2000 Trial - A reliable assessment of the efficacy and safety of donepezil and aspirin in Alzheimer's Disease

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

What was the AD2000 study?

AD2000 was a large, simple, 'real-life' trial that aimed to produce reliable evidence on the value of donepezil (Aricept®) in routine practice. Previous randomised trials, among patients with mild to moderate 'probable Alzheimer's disease', have established that donepezil can improve performance in cognitive function tests, but with no evidence that the drug reverses the underlying disease process. It was also not clear how the drug affects the day-to-day functioning, or behavioral disturbance, its impact on the quality of life of the patient and their carer.

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. To investigate whether aspirin delays progression of dementia, suitable patients were further randomised to receive daily aspirin or to avoid aspirin. 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.

What were the results of the study?

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 can not 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.

Publications

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. (http://www.thelancet.com/)

(This is a link to the Lancet website. You must register, or be registered with the Lancet already, to view the Article and Commentary. Registering is a very quick process).

AD2000 Abstracts

- **Twelve-week response to cholinesterase inhibitors does not predict future benefit: the ad2000 trial experience (/Documents/college-mds/trials/bctu/ad2000/stockholm-abstract.pdf)**
- **Drop-Out Bias Undermines Findings Of Improved Functionality With Cholinesterase Inhibitors (/Documents/college-mds/trials/bctu/ad2000/stockholm-abstract-2.pdf)**
- **Cognition is a Poor Predictor of the Costs of Care in Alzheimer's Disease (/Documents/college-mds/trials/bctu/ad2000/seville-cognition-abstract-0503.pdf)**
- **Functionality, Behaviour and Age, but not Cognition or Donepezil Treatment, Predict Institutionalisation in Alzheimer's Disease (/Documents/college-mds/trials/bctu/ad2000/seville-cognition-abstract-0503.pdf)**
- **Effect of Aspirin on the Progression of Alzheimer's Disease (AD) (/Documents/college-mds/trials/bctu/ad2000/ad-article.pdf)**
- **Effects of Discontinuing Donepezil Treatment on Cognition and Function in Patients with Alzheimer's Disease (/Documents/college-mds/trials/bctu/ad2000/age-ageing-0206.pdf)**

Other information

- **AD2000 Results Press Release (/Documents/college-mds/trials/bctu/ad2000/press-release-250604.pdf)**
- **NICE responds to judicial review outcome 10th August 2007 (/Documents/college-mds/trials/bctu/ad2000/nice-incourt-press-statement.pdf)**
- **Summary of AD2000 Results for Health Care Professionals (/Documents/college-mds/trials/bctu/ad2000/AD2000-lancet-results-hcpRG220604.pdf)**
- **Summary of AD2000 Results for Patients and Carers (/Documents/college-mds/trials/bctu/ad2000/patient-carer-newsletter.pdf)**