INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY
Int. J. Geriat. Psychiatry **15**, 50–53 (2000)

SUSTAINED COGNITIVE IMPROVEMENT FOLLOWING TREATMENT OF ALZHEIMER'S DISEASE WITH DONEPEZIL

MAVIS EVANS,[1]* ANDREW ELLIS,[2] DAVID WATSON[3] AND TAFIKA CHOWDHURY[4]
[1]*Consultant Psychogeriatrician and Clinical Director, Elderly Mental Health Directorate, Wirral and West Cheshire Community NHS Trust, Clatterbridge Hospital, Bebington, UK*
[2]*Consultant Psychogeriatrician, EMH Directorate, WWCCT, Clatterbridge Hospital, Bebington, UK*
[3]*Specialist Registrar, EMH Directorate, WWCCT, Clatterbridge Hospital Bebington, UK*
[4]*Staff Grade Psychiatrist, EMH Directorate, WWCCT, Clatterbridge Hospital, Bebington, UK*

ABSTRACT

Objectives. To audit response to the anticholinesterase inhibitor donepezil in patients referred to a specialist memory clinic, to identify possible means of targeting the drug more accurately.

Design. All referrals to the clinic who were assessed and treated against a protocol, with structured follow-up.

Subjects. All referrals of any age with the diagnosis of probable Alzheimer's disease, mild to moderately severe.

Main outcome measures. Cognitive improvement as measured by serial ADAS-cog and MMSE examinations.

Results. Two hundred and eight-two patients commenced on treatment, improved cognitive functioning in over 65% of patients reaching 3 months ($N = 184$), 51% on intention to treat analysis ($N = 231$), with significantly greater improvement ($p = 0.03$) in those aged 65 and under. Carer reports of behavioural improvement not always linked to cognitive improvement. Trend to increased response in those on concomitant antidepressants.

Conclusion. Three-month assessment for response prior to agreeing continuation of treatment selects a group who maintain their response. Younger patients should be targeted for early assessment and treatment.

KEY WORDS—Alzheimer's disease; donepezil; targeting; early onset dementia

The anticholinesterase inhibitor donepezil (Aricept) was licensed in April 1997, causing much controversy over its prescription within the UK National Health Service. It was the first widely marketed anticholinesterase inhibitor; prior to its release there was no recognized treatment for cognitive impairment other than social support and symptomatic treatment for associated problems (Evans, 1998).

Different purchasers of health care have different priorities: the introduction of the drug has been uneven, with some areas funding a managed and closely audited option, others allowing piecemeal prescription with differing criteria for assessment and treatment, thus making audit difficult, and others offering no extra funding.

A protocol was developed and agreed between Clatterbridge Hospital and the health authorities, and prescribing by consultants commenced in November 1997. The protocol is in line with the Standing Medical Advisory Committee (1998) report on donepezil in that it requires evidence of efficacy after 3 months' treatment before the prescription is continued. It uses similar inclusion criteria to the original trials, ie probable Alzheimer's disease (NINCDS–ADRDA criteria; McKhann *et al*., 1984) and Mini-Mental State Examination (MMSE) score of 10–26. A specialist memory clinic was developed and began in April 1998, using the same assessment tools and protocol that had been in place from November 1997.

Placebo-controlled treatment trials of donepezil have shown clinical efficacy in treating the symptoms of Alzheimer's disease—a key requirement in obtaining its licence (Rogers *et al*., 1998a,b; Rogers and Friedhoff, 1998). The data seem to show three main types of response to the medication: no change, possible slowing of expected deterioration, and improvement in symptoms. In view of the total

*Correspondence to: Mavis Evans, Elderly Mental Health Directorate, Wirral and West Cheshire Community NHS Trust, Clatterbridge Hospital, Bebington, Wirral CH63 4JY, UK.

CCC 0885–6230/2000/010050–04$17.50

Received 1 March 1999
Accepted 17 June 1999

number of patients in the catchment area with Alzheimer's disease, it was decided to restrict continuation to those patients showing improvement of four or more points on the ADAS-cog (Rosen *et al*., 1984). This was felt to be the most cost-effective method of prescription and has enabled us to offer treatment under the same criteria to all those referred to the clinic.

As donepezil has been licensed to treat the cognitive losses associated with Alzheimer's disease, it was felt that cognitive improvement must be the criterion used to decide continuation or withdrawal of treatment. However, activities of daily living (ADLs) and behaviour are probably more socially and clinically relevant endpoints (*Drug and Therapy Bulletin*, 1998) leading to questions of whether drug treatment is an appropriate use of resources for the elderly compared with nursing and social support and if improvement in ADAS-cog necessarily correlates with improved function (Bentham *et al*., 1998).

METHOD

Patients are referred for assessment and treatment by hospital consultants or their general practitioners (primary care physicians).

As donepezil is currently licensed for mild to moderate disease only, the exclusion criterion of MMSE < 10 is used. Patients are usually able to understand their diagnosis and its implications, so an important function of the clinic is counselling and support for patients and their carers. The patients may need repeated explanations and more time to communicate their worries and fears, but they have the ability, given this time, to participate in the decisions being made about their future treatment.

At every assessment, the MMSE, Bristol ADL scale, Behave-AD and a rating of carer stress are given, together with the ADAS-cog at initial assessment and at 3- and 12-month follow-up.

Treatment given is donepezil 5 mg daily. When prescribing commenced there was no evidence that a 10 mg dose gave significantly greater benefit, but the increased cost meant that fewer patients could be offered treatment. The decision was therefore made by the clinicians involved not to increase the dose.

RESULTS

Two hundred and eighty-two patients have commenced treatment, ages 44–91; 47 were withdrawn due to intolerable side-effects or non-compliance and 184 have reached 3-month assessment. Of these, 119 improved an average of seven points on the ADAS-cog, 65 deteriorated an average two points (range -22 to $+23$). Eighty-four patients have reached 6 months of treatment, 61 patients 9 months, 40 12 months, 19 15 months and five 18 months under this protocol. Cognitive improvement is being maintained (Table 1).

Younger age groups showed a greater improvement than the group as a whole, this reaching significance ($p = 0.003$) in those patients aged under 65 (Mann-Whitney/Wilcoxon two-tailed test). There was no significant difference in response between male and female patients ($p = 0.27$). Patients on concomitant antidepressants (all SSRIs) showed a trend to improved response, but

Table 1. Sustained response to treatment in selected groups of responders

Visit	*N*	MMSE	ADAS	(*N*)	MMSE	ADAS
0	282	19.1	25.8			
		Responders			Non-responders	
0	119	19.1	26	65	19.1	24.4
3/12	119	21.8	19.3	65	18.9	26.6
6/12	84	20.3				
9/12	61	20.7		47: stopped < 3/12, s/e or non-compliance		
12/12	40	20	22.4	51 not yet to 3 months		
15/12	19	19.5				
18/12	5	21.7				

numbers were small and this did not reach significance.

Clinically, both professionals and carers are noting improvements in behaviour. Surprisingly, these are not always linked to cognitive improvement. It must be remembered, however, that the behavioural questionnaire is subjective, and the initial improvement reported in the majority of patients probably relates as much to the support and counselling received from the clinic as to actual improvement. Therefore quantification of these changes is difficult, but such improvements are obviously of great importance to carers and need further investigation.

KEYPOINTS

- Donepezil treatment shows cognitive improvement in 51% of those who commence treatment, or 65% of those who are compliant to 3 months
- Cognitive improvement in the selected group of responders was maintained over 12 months
- Behavioural improvement is often reported by carers and is sometimes independent of cognitive improvement
- Support and counselling of patient and carer is an important component of treatment, and may contribute to the subjective reporting of behavioural improvement

DISCUSSION

The economic burden of providing for increasing numbers of elderly people requiring social care has major resource implications for the health and social services (Holmes *et al*., 1998). Institutional care carries the greatest cost, cognitive impairment is one of the most common reasons for entering a home and further longitudinal studies of these treatments are vital to assess impact on need for and length of such care.

The improved results seen in younger age groups, where one could assume the presence of a more severe form of the disease, may seem surprising. However, late onset Alzheimer's disease has been shown to have an increased incidence of white matter lesions and an association with previous hypertension (Snowdon *et al*., 1997; Skoog, 1997). It may be that this subtype has a worse prognosis to anticholinesterase inhibitors.

An as yet unanswered question is when treatment should be withdrawn in patients who have originally responded. The open label extension study (Rogers and Friedhoff, 1998) shows improvements are sustained at the same magnitude for almost 2 years; earlier trials appear to show that withdrawal of the drug leads to cognitive losses back to that of the parallel placebo group over a 4–6 week period (Rogers *et al*., 1998b). In practical terms, this rapid deterioration could lead to a crisis and perhaps admission to hospital or residential care as an elderly carer is overwhelmed. How can we tell if the drug is having any residual effect once the patient has become severely demented? A trial of withdrawal would seem unethical—will the response be regained if treatment is reinstated? Will the carer have lost confidence during the withdrawal period and remain unable to cope? Can society afford to continue prescribing these drugs if the benefit has probably been lost? With a finite drug budget, would another patient derive more benefit?

Rivastigmine (Exelon) is being (and other future drugs will be) introduced under the same protocol to assess efficacy and establish their place in the treatment of this distressing disease.

The cholinesterase inhibitors have gained their licences for showing improvement in cognitive functioning. While this is an important feature, future use of the drugs may show the behavioural improvement to be of greater clinical importance: global functioning rather than cognitive changes should be investigated more closely. Practising clinicians are aware that psychotic features and behavioural disturbances are more likely to lead to entry into care than poor memory and disorientation.

CONCLUSION

Resources for the NHS are finite. The concept of cost-effectiveness is here to stay: doctors must be willing to practise clinical audit leading to evidence-based medicine and to look for means of targeting treatment to the better responders, to justify the increased cost of new treatments.

NOTE ADDED TO PROOF

Up to the end of November 1999 over 400 patients have been assessed at the clinic and 363 com-

menced on treatment (60 on rivastigmine). Approximately half of those commenced on treatment show an improvement of 4 or more points on ADAS-cog at twelve weeks, and so continue on treatment. Of those on donepezil, 53 have reached 48 weeks and 35, 60 weeks of treatment: both of these groups still show average MMSE and ADAS-cog scores equivalent to those at baseline (MMSE 19.5 cf 19.4 baseline; ADAS-cog 24.3 cf 25.4 baseline). This targeted group therefore show a sustained response to treatment without the expected deterioration shown by this disease. Numbers assessed within the clinic make it unlikely that this is an artefact.

Full data and differentiation between the two drugs will be given in a future paper.

ACKNOWLEDGEMENTS

Steve Taylor, EMI Academic Unit, Wirral, for statistical help.

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