Donepezil Only Marginally Improves Outcomes in Alzheimer's Disease

Courtney C, Farrell D, Gray R, et al. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomized double-blind trial. Lancet 2004;363:2105–15.

Study Overview

Objective. To determine if donepezil improves clinical outcomes in patients with Alzheimer's disease.

Design. Randomized, double-blind, placebo-controlled trial with an intention-to-treat analysis.

Setting and participants. Eligibility criteria included patients referred to a memory clinic with a presumptive diagnosis of Alzheimer's dementia. Diagnoses were made using a routine examination and a diagnostic checklist based on the DSM-IV diagnosis of dementia of Alzheimer's type. Further eligibility criteria included having a regular caregiver, currently living within the community (not institutionalized), and not currently taking a cholinesterase inhibitor. Patients with potential contraindications to donepezil were excluded.

Intervention. Eligible patients were initially randomized to either donepezil (5 or 10 mg per day) or placebo for an initial 12-week run-in period. After the run-in period, patients were again randomized to either donepezil (5 mg or 10 mg) or placebo and treated for 48 weeks. For the purposes of the analysis, both donepezil groups were combined. The study was modified to allow individuals to continue with the trial if they chose. After each 48-week treatment period, patients would be given a 4- to 6-week washout period and then be allowed to continue treatment for an additional 48 weeks, remaining on the treatment arm to which they had been initially allocated.

Main outcome measures. The primary endpoint for this study was entry into institutional care and progression of disability. Progression of disability was defined as loss of either 2 of 4 basic activities or 6 of 11 instrumental activities on the Bristol Activities of Daily Living Scale. Secondary outcomes include functional ability (measured using the Bristol Activities of Daily Living Scale); presence and severity of behavioral and psychologic symptoms and signs of dementia (measured using the Neuropsychiatric Inventory); cognition (as measured by the Mini-Mental State Examination [MMSE]); progression to severe cognitive disability (MMSE < 10); psychologic well-being of the patient's caregiver (measured using the General Health Questionnaire); serious adverse events; medication withdrawals; and death from Alzheimer's disease. Another secondary aim of the study was to determine the cost-effectiveness of donepezil treatment for Alzheimer's disease. This was measured as the additional cost per day of moderate disability avoided through donepezil therapy.

Main results. 566 patients were initially randomized, and 511 patients completed the 12-week run-in period. Baseline characteristics were similar between the 2 groups. 486 patients (242 allocated to donepezil and 244 to placebo) entered the first-phase treatment period. No significant difference was seen in rates of institutionalization between the donepezil and placebo groups at either 1 year (9% versus 14%; $P = 0.15$) or 3 years (42% versus 44%; $P = 0.4$). The relative risk of entering institutional care for the donepezil group was 0.97 (95% confidence interval, 0.72–1.30) compared with the placebo group. Progression to disability was also similar between the donepezil and placebo groups at 1 year (13% versus 19%; $P = 0.3$) and 3 years (55% versus 53%; $P = 0.9$). During the first 12 weeks, baseline MMSE scores improved by 0.9 points in the donepezil group while no improvements were seen in the placebo group. After the first 12 weeks, MMSE scores deteriorated at a similar rate in both groups. No differences were seen in the development of severe cognitive disability, in either behavioral or psychologic symptoms, or in Alzheimer's-related death or serious adverse events between the 2 groups. The estimated annual cost per patient for treatment was greater in the donepezil group when compared with the placebo group, although this difference was not statistically significant.

Conclusion. Treatment of Alzheimer's disease with donepezil does not affect clinically important outcomes, such as progression to disability or institutionalization. Furthermore, this approach may be even more costly than noncholinesterase inhibitor–based therapy.

Commentary

Alzheimer's disease is a common and debilitating condition

[1]. The costs for caring for a patient with Alzheimer's are high, both financially and with regards to a caregiver's time and psychologic well-being [2,3]. As population demographics for developed countries demonstrate an aging population, this disease is likely to exact a substantial toll on society. Few effective treatments exist to slow the progression of Alzheimer's disease. Cholinesterase inhibitors have been marketed for the treatment of Alzheimer's for several years. Randomized controlled trials have demonstrated that these drugs result in improved scores on cognitive tests over the short term (3 months to 12 years) [4,5]. Data are lacking on how effective these drugs may be on long-term disease progression and on more relevant endpoints, such as progression to severe impairment or institutionalization.

This study by Courtney et al was designed to attempt to answer these questions. Although the study was significantly reduced in size from 3000 to 500 participants due to accrual problems, it still had reasonable power to answer some of these questions. Furthermore, an additional strength of the study was that it followed patients for a substantial period of time, with well over half of the patients being followed for at least 1 year. The overall result was that donepezil had little effect over placebo. The authors also evaluated the cost-effectiveness of donepezil therapy; it was found not to be cost-effective. This is hardly surprising given that donepezil is an expensive drug and it resulted in little improvement in clinical outcomes.

Applications for Clinical Practice

Although donepezil may slightly improve scores on cognitive tests, it does not appear effective at improving more clinically relevant endpoints in patients with Alzheimer's disease. Donepezil treatment does not appear to be cost-effective.

–Review by Harvey J. Murff, MD, MPH

References

1. Kukull WA, Higdon R, Bowen JD, et al. Dementia and Alzheimer disease incidence: a prospective cohort study. Arch Neurol 2002;59:1737–46.
2. Leon J, Neumann PJ. The cost of Alzheimer's disease in managed care: a cross-sectional study. Am J Manag Care 1999;5:867–77.
3. Markowitz JS, Gutterman EM, Sadik K, Papadopoulos G. Health-related quality of life for caregivers of patients with Alzheimer disease. Alzheimer Dis Assoc Disord 2003;17:209–14.
4. Trinh NH, Hoblyn J, Mohanty S, Yaffe K. Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease: a meta-analysis. JAMA 2003;289:210–6.
5. Lanctot KL, Herrmann N, Yau KK, et al. Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. CMAJ 2003;169:557–64.