Long-term Treatment of Mild to Moderate Alzheimer Disease in a 77-Year-Old Female Patient

Patrick Gillette, MD, CMD

Alzheimer disease is characterized by a loss of cholinergic neurons in the basal forebrain and a decrease in acetylcholine levels.[1] Currently, cholinesterase inhibitors, drugs that act by inhibiting the enzyme responsible for the hydrolysis of acetylcholine, are the only therapy for the treatment of Alzheimer disease approved by the Food and Drug Administration. The cholinesterase inhibitors have been shown to be effective in treating the cognitive symptoms of Alzheimer disease and in slowing functional decline.[2–6] An early diagnosis of Alzheimer disease allows initiation of cholinesterase inhibitor therapy early in the disease course and could serve to lengthen the time during which the patient can function independently. The benefits of early diagnosis and initiation of long-term cholinesterase inhibitor therapy are illustrated in the case of a 77-year-old woman residing in an assisted-living facility who had cognitive impairment. Mild Alzheimer disease was subsequently diagnosed and treated with a cholinesterase inhibitor for 3 years.

Case Report

A 77-year-old woman visited her physician in November 1997 with a chief complaint of forgetfulness noticed by friends and family members. Her medical history was remarkable for paroxysmal atrial fibrillation, hypertension, and a hysterectomy for endometrial adenocarcinoma. She had no history of coronary heart disease or stroke, and she walked regularly. Findings of the physical examination were otherwise unremarkable. The patient was taking several medications, including estrogen (0.625 mg/d, since 1991), atenolol (25 mg/d), lisinopril (2.5 mg/d), vitamin E (1200 IU/d, since 1998), and *Ginkgo biloba* (120 mg/d, since 1998). There was a family history of dementia.

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From the Rogue Valley Manor (PG), Medford, Ore. Address reprint requests to Patrick Gillette, MD, CMD, Rogue Valley Manor, 1200 Miramar Ave, Medford, OR 97504.

A complete medical work-up was initiated because of the patient's complaint of chronic forgetfulness. Laboratory tests, including a complete blood count, serum chemistries, rapid plasma reagin, vitamin B_{12} and folate levels, and thyroid function tests, were normal. A computed tomographic scan showed age-related atrophy but was otherwise negative. A Mini-Mental State Examination (MMSE) was administered to assess cognition, and the patient scored 23 of 30, indicative of cognitive impairment. In addition to her memory loss, the patient exhibited language difficulties, consistent with aphasia, and difficulty recognizing familiar objects, consistent with agnosia.

Based on these findings, a diagnosis of probable Alzheimer disease was made in November 1997. After careful consideration of the diagnosis and the patient's treatment options, donepezil was initiated at 5 mg/d in February 1998. Based on tolerability and a low incidence of side effects, the dose was increased to 10 mg/d after 4 weeks. The drug continued to be well tolerated, and no serious side effects were noted. In January 1999, after approximately 11 months on donepezil, the patient's MMSE score had improved to 27.

In late January 1999, despite an improved MMSE score, the patient stopped taking donepezil because neither she nor her niece noticed further improvement. Three weeks after discontinuing donepezil, however, the patient experienced a disturbing incident. She reported that she had discovered the telephone off the hook and picked up the receiver but failed to recognize this familiar object. At the patient's request, donepezil treatment was resumed at the end of February 1999 (5 mg/d, increased to 10 mg/d after 4 weeks). In October 1999, 8 months after resuming treatment with donepezil, her MMSE score was 26.

A comprehensive follow-up physical examination was performed in April 2000. In addition to probable Alzheimer disease, the patient had hypertension and chronic atrial fibrillation. The patient had already had chronic atrial fibrillation diagnosed

and treatment with coumadin (3 mg/d) was started in March 2000. In November 2000, after receiving donepezil (10 mg/d) for a total of 32 months, her MMSE score was 29.

Three and one-half years after the initial treatment with donepezil, the patient is living independently in a retirement community. Despite the community's affiliation with an assisted-living facility, the patient has maintained an independent living arrangement. She shops and prepares her own meals. Although she was able to drive extensively and passed the driving tests required every 6 months in the state of Oregon for 3 years after her diagnosis, she stopped driving in the spring of 2001.

Discussion

This case illustrates the value of a proactive approach to diagnosing Alzheimer disease and the importance of initiating treatment early in the disease course. This case also shows that the diagnosis and treatment of Alzheimer disease can be managed in a primary care setting. Cognition can be reliably assessed using the MMSE, and with proper training, the MMSE can be administered by medical assistants.

Clinical studies have shown that the cognitive and functional decline associated with Alzheimer disease is attenuated by treatment with cholinesterase inhibitors.[2,4–7] Optimal clinical benefits from cholinesterase inhibitors have been reported when treatment is initiated early, continued without interruption, and maintained long term.[3,8] Without treatment, MMSE scores in Alzheimer disease patients have been shown to decrease 2 to 4 points each year.[9] An attenuation of the expected decline in MMSE scores represents a positive and clinically meaningful treatment outcome in a degenerative disorder such as Alzheimer disease. Some patients, however, including the one described in this case, show improvements in cognitive function in response to cholinesterase inhibitor therapy. In fact, in one study, a 4-point improvement from baseline was observed in ADAS-cog scores, an instrument routinely used to measure cognitive performance in clinical trials, in more than 50% of patients after receiving 10 mg/d of donepezil for 6 months.[2]

Early detection and early treatment might have helped this patient maintain the independent lifestyle she had always enjoyed. Delaying treatment initiation in this patient could have resulted in further cognitive and functional decline, with a corresponding increase in the degree of care required. Based on clinical trial data and several years of clinical experience, it is now recognized that patients stand to gain maximal treatment benefit when therapy is initiated early in the disease course. Treatment benefits can also be enhanced when patients and their caregivers are involved in making treatment decisions, particularly when the disease is in the early stages. This patient has been involved in making treatment decisions and is well informed about the disease and current treatment options. For most Alzheimer disease patients, however, the caregiver will often be more involved in making treatment decisions than the patient.

Prolonging the period during which the patient is able to maintain cognitive and functional ability has far-reaching ramifications for the patient's quality of life. While this case represents the ideal, stabilization of symptoms or slowing the rate of further decline is the most likely outcome of treatment. In a degenerative disease such as Alzheimer disease, these outcomes are regarded as treatment success. Given the cognitive, functional, and behavioral benefits, all patients with a diagnosis of mild to moderate Alzheimer disease should at least be given a trial of cholinesterase treatment.

It is important to note that although this patient regained treatment benefits despite a 3-week treatment interruption, optimal benefits are derived from long-term, uninterrupted therapy. A recently published open-label extension study showed that when cholinesterase inhibitor therapy was interrupted for 6 weeks, treatment effects on cognition were lost and failed to recover fully when the drug was reinitiated.[8] This finding illustrates the value of educating patients and caregivers about the benefits of cholinesterase inhibitors and the importance of establishing realistic expectations regarding treatment outcomes. Patients and caregivers should be made aware that although cholinesterase inhibitor therapy has been shown to result in improvements in cognition, attenuation of further decline is also considered a positive treatment outcome. Although the treatment outcomes observed in this patient represent the ideal, this type of response is not likely to be observed in most patients. Establishing realistic expectations of treatment outcomes can therefore serve to decrease the number of patients

who discontinue therapy prematurely because of a perceived lack of efficacy.

References

1. Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: a review of progress. J Neurol Neurosurg Psychiatry 1999;66:137–47.
2. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. Neurology 1998;50:136–45.
3. Winblad B, Engedal K, Soininen H, et al. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. Neurology 2001;57:489–95.
4. Rosler M, Anand R, Cicin-Sain A, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. BMJ 1999;318:633–8.
5. Raskind MA, Peskind ER, Wessel T, Yuan W. Galantamine in AD: a 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. Neurology 2000;54:2261–8.
6. Mohs RC, Doody RS, Morris JC, et al. A 1-year placebo-controlled preservation of function survival study of donepezil in AD patients. Neurology 2001;57:481–8.
7. Burns A, Rossor M, Hecker J, et al. The effects of donepezil in Alzheimer's disease—results from a multinational trial. Dement Geriatr Cogn Disord 1999;10:237–44.
8. Doody RS, Geldmacher DS, Gordon B, Perdomo CA, Pratt RD. Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer disease. Arch Neurol 2001;58:427–33.
9. Gray J, Gauthier S. Stabilization approaches to Alzheimer's disease. In: Gauthier S, editor. Clinical diagnosis and management of Alzheimer's disease. London: Martin Dunitz, 1994:261–7.