Update on Alzheimer Drugs (Donepezil)

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Background: Several clinical trials have been conducted over a period of many years reporting the benefits of donepezil for Alzheimer disease (AD) patients.

Review Summary: Randomized, double-blind, placebo-controlled studies of 3–6 months' duration have demonstrated significant benefits for 5 mg/D and 10 mg/D of donepezil compared with placebo. The results include benefits for cognition, activities of daily living, and abnormal behaviors associated with AD. The benefits are independently detectable by clinicians based upon direct patient assessment with input from a caregiver. Populations studied include mild-to-moderate AD patients, moderate-to-severe AD patients, nursing home patients, and outpatients. Open label studies that took place after the double-blind phase and 1-year double-blind, placebo-controlled trials demonstrated that benefits persist for more than a year. Adverse event (AE) profiles, generated in studies that used a 1-week forced dose titration, show a low incidence of primarily cholinegic AEs such as nausea and diarrhea. There are no significant laboratory AEs or drug interactions. Recent studies have assessed the benefits of donepezil in patients with ischemic vascular dementia, mild cognitive impairment, and other cognitive disorders.

Conclusions: Donepezil benefits AD patients by improving, stabilizing, or retarding decline of the cognitive, functional, and possibly behavioral features of the disease. The duration of benefits is not known but extends beyond 1 year. The drug is safe and well tolerated.

Key Words: Alzheimer disease, treatment, donepezil

(*The Neurologist* 2003;9: 225–229)

DONEPEZIL

Chemical Structure and Rationale for Development

Donepezil, (R,S)-1-benzyl-4[(5,6 dimethoxy-1-indanon)-2-yl]-methyl piperidine hydrochloride, is a synthetic drug designed to selectively and reversibly inhibit acetylcholinesterase (AChE). Its piperidine structure distinguishes it from the acridines (i.e., tacrine) that have been associated with hepatotoxicity, as well as from the carbamates (i.e., physostigmine, rivistigmine). Although both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) occur in the brain, acetylcholinesterase is involved in synaptic transmission and is the primary therapeutic target for drug treatment designed to enhance synaptic availability of acetylcholine.[1] Microglial-derived butyrylcholinesterase increases in the brain as Alzheimer disease (AD) advances,[2] but it is not clear whether this phenomenon contributes to the causes or consequences of AD. While AChE is normally the most abundant cholinesterase in the brain, BChE predominates in peripheral tissues, such as gastrointestinal (GI) and cardiac smooth muscle, and is believed to mediate at least some of the GI side effects seen with less selective agents.[3] The selectivity of donepezil for AChE over BChE is approximately 1,000-fold.[3]

Evidence for Efficacy

Preclinical Data

The first type of evidence for efficacy comes from studies demonstrating that donepezil is an effective acetylcholinesterase inhibitor (AChEI). Investigations have demonstrated a good correlation between red blood cell inhibition of AChE and central cortical levels of inhibition.[4] Plasma concentrations of donepezil are dose-related and approach a plateau at plasma concentrations of 50 ng/ml, corresponding to 80–90% enzyme inhibition.[5] Mean percentage inhibition (± SEM) at a dose of 5 mg/d and 10 mg/d are 63.9% ± 0.9% and 74.7% ± 1.2%, respectively.[5] Benefits on the Alzheimer Disease Assessment Scale-cognitive subscale (ADAScog) and Clinician's Interview-Based Impression of Change (CIBIC-plus) correlate well with both plasma concentrations of donepezil and with RBC AChE inhibiton.[5] A recent study provides evidence for donepezil's dose-dependent inhibition of AChE in the brain, with maximal effects seen in the cortex and hippocampus.[6] In aged animals and in animal models of cholinergic deficiency, donepezil improves cognitive performance compared with placebo.[7]

In double-blind, placebo-controlled studies of patients with AD, donepezil benefits cognition, function, and noncognitive behavior.

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1074-7931/03/0905-0225
DOI: 10.1097/01.nrl.0000087723.53475.48

Clinical Efficacy Data

Cognition and Global Measures

In double-blind, placebo-controlled studies of patients with AD, donepezil benefits cognition, function, and noncognitive behavior, with benefits clearly still present at the end of the longest studies lasting 1 year.[5,8–12] In shorter studies lasting 12–24 weeks, donepezil-treated patients show improvement over their baseline scores on psychometric and global measures, while placebo-treated patients show mild decline.[5,8,9,12] Because the studies are short and the disease is heterogeneous, most patients change on only a few items on any given scale, yielding small average point changes compared with placebo on scales such as ADAScog and Mini-Mental Status Examination (MMSE). These changes are, however, clinically detectable as measured by a clinical global scale (CIBIC–Plus), which assesses cognition, behavior, and functioning directly by assessing the patient along with input from the caregiver. The point differences on cognitive tests, although small in absolute value, are quite consistent across studies conducted in multiple countries carried out in multiple languages and cultures. There is good evidence that all patients benefit from short-term (up to 6 months) of donepezil treatment (Fig. 1). In cumulative response analyses the curve representing change from baseline on ADAScog scores shows that drug treatment shifts such curves to the left, that is, fewer donepezil-treated patients decline and more stabilize or improve during the observation period compared with placebo treated patients, with no overlap of the curves comparing drug to placebo.[8] The degree of benefit may vary between patients and is not predictable in advance of therapy. Donepezil has shown benefit on all of the cognitive and global scales assessed to date, which include the ADAScog, MMSE, Severe Impairment Battery, CIBIC–Plus and Gottfries-Bråne-Steen scale (see[13] for a discussion of many of these instruments).

Functioning

Donepezil benefits patient functioning in 3-month,[5] 6-month,[8] and 12-month studies[11] including 1 study with a unique design that sought to measure the stabilization of functional ability.[10] In the early studies, the Clinical Dementia Rating (CDR), scored by the sum of the boxes method (CDR-SB),[14] was employed to ascertain the effects of donepezil in the functional realm.[5,8] Donepezil-treated patients did better on the CDR-SB and, curiously, the effect for those treated with 10 mg/d did not fully reverse, even with a 6-week washout of the drug after the end of the study.[8] A retrospective analysis comparing decline in the activities of daily living (ADL) domains of the CDR across groups in the 30-week pivotal trial suggested less loss of ADL for patients on 10mg donepezil compared with 5 mg and placebo.[3] A later double-blind, placebo-controlled study employed the Interview for Deterioration in Daily Living Activities in Dementia (IDDD) scale, which includes both basic and complex activities scales.[9] The donepezil-treated patients showed benefits on the complex activities scale compared with placebo but not on the basic scale, likely because there was little movement on this scale in these mild- to-moderate patients over the

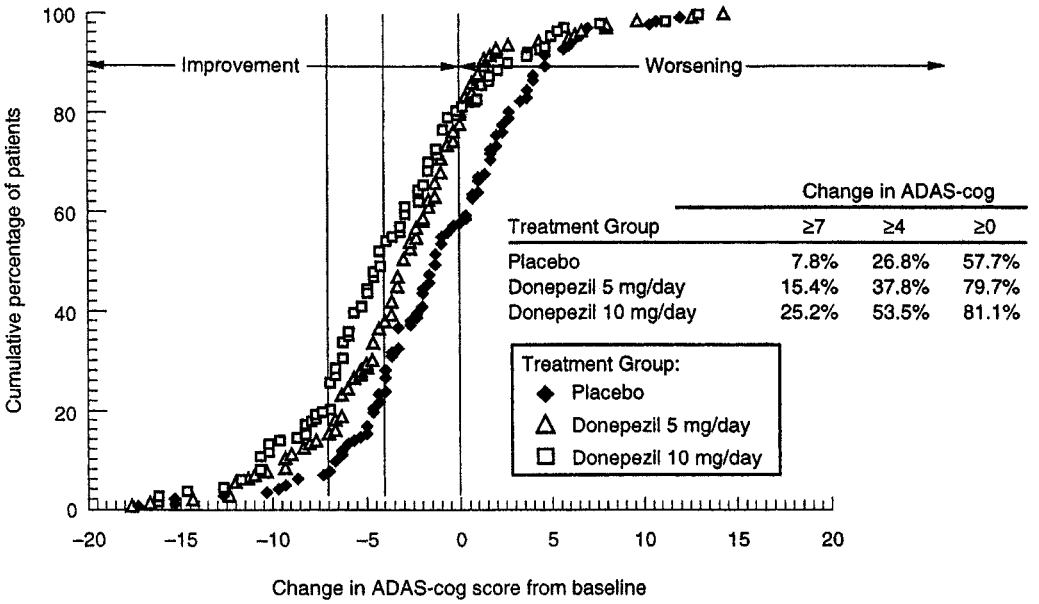

FIGURE 1. Cumulative percentage of patients with specified changes from baseline in ADAS-cog scores. (Reprinted with permission from: Rogers SL, Farlow MR, Doody RS, et al. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Neurology, 1998; 50:136–145.)

6-month study. A recent 6-month double-blind placebo-controlled study of patients with moderate to severe AD showed benefit for donepezil versus placebo on the Disability Assessment for Dementia scale (DAD) and the Functional Rating Scale (FRS).[12] A 1-year double-blind, placebo-controlled study employed the Progressive Deterioration Scale (PDS) and found a significant benefit for donepezil treatment on this scale at the end point.[11] Finally, a 1-year, double-blind, placebo-controlled study evaluated the time to clinically noticeable decline in donepezil treated versus placebo treated patients.[10] Decline was defined as loss or decline on 1 basic ADL or 10% (i.e., 2 items) of complex ADL on the Alzheimer Disease Functional Assessment and Change scale (ADFACS). The median time to loss of function for donepezil patients was, on average, 357 days compared with 208 days in the placebo group, a delay of about 5 months.

Behavior

Fewer studies have examined donepezil's effects on behavioral disturbances in AD, and none were designed with this as the primary outcome. Nevertheless, donepezil provides benefit in this realm as well. In a double-blind, placebo-controlled study involving mild- to-moderate nursing home patients, there was no difference between the drug and placebo treated patients on an abbreviated version of the Neuropsychiatric Inventory (NPI) after 6 months of therapy,[15] possibly related to the fact that both groups improved on the NPI. There was also little baseline behavioral pathology in either group, which could have been an artifact from using the shortened version of the NPI and/or a reflection of the fact that only mild- to-moderate subjects were recruited into the study. In contrast, in a double-blind, placebo-controlled study of patients with moderately severe AD, donepezil-treated patients showed average reductions in baseline NPI scores over the course of 6 months, while the placebo group stayed about the same.[12] The average NPI score at baseline did not differ between the groups and was approximately 19, with a wide range in both groups. Since this study did not select for the presence or severity of behavioral disturbances, its results reflect the behavioral benefits that can be expected in the average AD patient as opposed to patients in whom disturbed behavior is the prominent complaint. Other open label and uncontrolled studies suggest a benefit of donepezil for treating clinically significant behavioral disturbances in AD.[16,17]

Special Populations and Settings of Care

Donepezil has recently been tested in a double-blind, placebo-controlled trial of patients with moderate and severe AD with standardized MMSE scores (sMMSE) of 5–17 out of 30 at entry.[12] The standardized MMSE is identical to the usual version except that it provides administration and scoring instructions to the examiner. Donepezil-treated patients showed significant benefits at 6 months on every measure employed in the study, which included The Severe Impairment Battery, Clinician's Interview-Based Impression of Change, sMMSE, Disability Assessment for Dementia, Functional Rating Scale, and neuropsychiatric interview (discussed above).

In a separate 6-month, double-blind, placebo-controlled study of nursing home patients with mild-moderate AD, donepezil treatment resulted in better MMSE and CDR-SB scores compared with placebo.[15]

Recent case reports and uncontrolled studies suggest the possibility that donepezil might benefit patients who have clinically diagnosed dementia with Lewy bodies,[18,19] multiple sclerosis,[20] traumatic brain injury,[21] Tourette syndrome with ADHD,[22] delirium,[23] bipolar disorder,[24] and Down syndrome.[25] One small, double-blind, placebo-controlled crossover study showed little benefit for donepezil treatment in patients diagnosed with progressive supranuclear palsy and suggested that high doses of donepezil might worsen extrapyramidal signs in these patients.[26]

Ongoing studies are examining the use of donepezil for reducing the progression from mild cognitive impairment (MCI) to AD or for treating the symptoms of MCI. Two double-blind, placebo-controlled studies have recently been completed that showed significant improvement on the ADAScog for patients with probable and possible ischemic vascular dementia who received donepezil.[27,28]

Duration of Benefits

A drug for AD could be said to benefit patients for as long as a difference between drug-treated subjects and placebo-treated subjects is maintained. However, ethical issues regarding the use of placebo, especially in long-duration trials, make it virtually impossible to hold investigators to this gold standard for the demonstration of sustained benefit.[29] Two 1-year, double-blind, placebo-controlled studies discussed above clearly demonstrate that the duration of donepezil's benefits extends to 1 year.[10,11] There is no indication from the data that the benefits are abruptly lost after 52 weeks, so they may continue beyond 1 year. A retrospective study of patients participating in 4 AD centers who were and were not taking cholinesterase inhibitors showed that donepezil-treated patients had slower rates of annual MMSE decline compared with nonusers (and users of tacrine) after controlling for age, education, gender, and ethnicity.[30] This study extends the observation of continued benefits seen in clinical trials to a population of patients outside of clinical trials, with average follow-up on drug treatment of about 1 year.

Data from the open label extension phases of the randomized, double-blind, placebo-controlled trials provide limited evidence to address the question of duration of benefits. The open label trial that followed a Phase 2 donepezil study, in which doses of 3 mg and 5 mg were compared with

placebo, confirm the observation of maintenance above baseline ADAScog scores for at least 1 year.[31] Patients who remained in this study for 2 years, 3 years, and beyond declined more slowly than literature-based predictions on the ADAScog and CDR-SB, but very significant subject attrition (more than 70% by the second year of open label) limits interpretation of these data. The open label study that followed 2 Phase 3 studies testing 5mg and 10mg of donepezil and conducted in the United States provides another opportunity to examine effects beyond 2 years. This study also provides the opportunity to contrast patients who were treated more or less continuously with patients who underwent a complete washout of benefits as assessed by the ADAScog.[32] Again, at 1 year after baseline, the continuously treated patients were still maintaining baseline scores, although those who crossed over from placebo in the double-blind study to drug in the open label failed to catch up with those who had been taking drug all along. In contrast, those who washed out for 6 weeks following the double-blind achieved some improvement in scores after they were allowed to restart the drug but were below baseline by about 3 points at 1 year, indicating the possibility that stopping drug leads to loss of benefits that cannot be regained. Patients who had been on drug more or less continuously and remained in the study at 2 years after baseline (about 70% of those entering the open label) were still better off compared with literature-based predictions of ADAScog decline.[30]

A 4–6 week titration from 5 mg to 10 mg is the current clinical recommendation.

Tolerability

Donepezil is well tolerated with a low incidence of AE compared with placebo. Cholinergic AEs are mild and predictable, without laboratory abnormalities or drug interactions. In part, this tolerability may reflect the dual metabolism of donepezil by the kidney as well as by the liver (cytochrome P450 2D6 and 3A4). In Phase III registration studies in which a forced dose escalation from 5mg to 10mg occurred at 1 week, the AEs that occurred significantly more often in drug compared with placebo were (5 mg: %, 10 mg: % versus placebo: %); nausea (7%, 22% versus 8%); insomnia (8%, 18% versus 5%); and diarrhea (6%, 13% versus 3%) in 1 study[5] and diarrhea (9%, 17% versus 7%); nausea (4%, 17% versus 4%); muscle cramps (6%, 8% versus 1%); and fatigue (5%, 8% versus 2%) in another.[8] Subsequent studies have reported similar findings as well as a low but significant incidence of vomiting (16%, 4% versus 4%) in a study that used a 1-week dose escalation[9]and vertigo (NA, 8% versus 2%); asthenia (NA, 8% versus 4%); and syncope (NA, 6% versus 3%) in a 1-year study.[11] This study, which used a 4-week titration, found reduced AE rates for those randomized to10 mg compared with the previous studies, which used rapid titration. AE (versus placebo) were nausea (11% versus 9%), insomnia (10% versus 7%), diarrhea (7% versus 7%). A 4–6 week titration from 5 mg to 10 mg is the current clinical recommendation. When donepezil is given at bedtime, vivid dreams and nightmares can occur. These adverse events were likely grouped under "insomnia" in the clinical trials, so specific frequencies are not known, but changing the dose to morning usually resolves the problem. An early report of a possible interaction between donepezil and paroxetine based upon clinical observation in 2 cases without pharmacodynamic studies[33] has not been substantiated, and donepezil has been widely combined with multiple medications in open label studies as well as in general use. Formal interaction studies have shown no interactions with theophylline, cimetidine, warfarin, or digoxin.[33]

Benefits, particularly stabilization of cognition and function, are maintained beyond 1 year.

CONCLUSION

In conclusion, donepezil is a safe and effective therapy for AD. It improves cognition, function, and behavior in several studies utilizing several different measures. The average drug versus placebo benefits on psychometric test scores are small. This may reflect the heterogeneity of the disease whereby not every item on the scale applies to every patient. The benefits of therapy, however, seem to extend to all treated patients. One cannot predict in advance whether a patient will respond by slower decline, stabilization, or improved test scores. Benefits, particularly stabilization of cognition and function, are maintained beyond 1 year, but the average maximal duration of benefits is not known. Delays in initiating therapy and long interruptions (i.e., 6 weeks) in treatment may lead to overall reductions of benefits for any given patient. No study so far has demonstrated that the benefits of the drug are definitely lost over time. Donepezil can safely be combined with most other drugs.

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