Drug Review

High-dose Donepezil (23 mg/day): A Step Forward for the Treatment of Moderate and Severe Alzheimer’s Disease

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Introduction

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder affecting 35 million people worldwide.1 Based on the latest estimates, more than half of these individuals would be classified as having moderate or severe AD.2 These advanced stages of AD extend over a period of several years and are often the most difficult for both patients and caregivers.

Only 2 agents are currently approved in for treatment beyond the mild to moderate stage—donepezil, an acetylcholinesterase inhibitor (AChEI), and memantine, a glutamate receptor antagonist that can be used alone or in combination with an AChEI. Progression of AD is inevitable, however, and cannot be halted by these therapy options, which address primarily the disease symptoms. Given the limited choices for therapy and the often devastating and prolonged impact of further decline in cognitive and functional abilities, additional options for treatment are urgently needed for this segment of the AD population. Studies shown that the cholinergic deficit is most evident in patients with more advanced symptoms.3 This suggests that the target level of cholinergic enhancement may change as symptoms progress. Patients in early stages of AD may achieve sufficient cholinergic stimulation from lower doses of AChEIs, while higher AChEI doses may be required in patients with more advanced AD. In 2010, the FDA approved a higher daily dose of donepezil (23 mg/day) for the treatment of AD in the moderate-to-severe stages based on positive results from a large, global, phase 3 clinical trial that compared switching to donepezil 23 mg/day with continuing treatment with donepezil 10 mg/day.4

Rationale for higher doses of donepezil

Positron emission tomography studies have shown that at stable doses of donepezil, 5 mg/d or 10 mg/d, average cortical acetylcholinesterase (AChE) inhibition was <30%.5,6 In a study in 61 Japanese patients with AD who were receiving a stable dose of donepezil 5 mg/d, a dose increase to 10 mg/d for 24 weeks was associated with more effective prevention of deterioration in severe AD.7 In a pilot study of patients with mild to moderate AD, higher doses of donepezil (15 mg/d and 20 mg/d) were reported to be safe and well tolerated.8 Based on those findings, doses of AChEIs that are higher than those currently approved might provide greater stabilization and/or symptomatic improvement in later stages of AD. A finding that increasing cholinesterase inhibition confers further benefits in moderate to severe disease, including in patients receiving combination therapy, would have implications for extending and/or improving AD treatment and significant value for public health9. The FDA approved donepezil, 23 mg/d, for patients with moderate to severe AD on the basis of phase III trial results.4,10

Pharmacokinetics

Peak plasma concentration is achieved for donepezil 23 mg tablets in approximately 8 hours, compared with 3 hours for donepezil 10 mg tablets. Peak plasma concentrations were almost two-fold higher for donepezil 23 mg tablets than donepezil 10 mg tablets.
10 mg tablets.

**Clinical results**

In a 24-week 10 randomized, double-blind, global, head-to-head clinical trial, patients with moderate to severe AD (MMSE, 0-20) on a stable donepezil 10 mg/d regimen for ≥ 3 months were randomized to increase their dosages to the once-daily donepezil 23 mg tablet or to be maintained on the 10 mg/d dose. Patients in the donepezil 23 mg group showed a statistically significant improvement in cognition as measured by the severe impairment battery (SIB) compared with donepezil 10 mg. Among the total study population (MMSE, 0-20), significant incremental benefit on the Clinician’s Interview-Based Impression of Change Plus Caregiver Input scale (CIBIC+ global function rating) was not seen with donepezil 23 mg/d versus donepezil 10 mg/d over 24 weeks of treatment.

This 24-week study demonstrated that treatment with donepezil 23 mg tablets can provide additional cognitive benefit in patients with moderate to severe AD compared with 10 mg donepezil, and its findings are consistent with previous analyses showing greater benefit with 10 mg than with 5 mg. A post hoc analysis was conducted using data from a 24-week, randomized, double-blind trial comparing donepezil 23 mg/day versus 10 mg/day in 1,467 patients with moderate to severe AD [baseline Mini-Mental State Examination (MMSE) score 0 to 20] 10. In the full study population, statistically significant incremental benefits of donepezil 23 mg/day over donepezil 10 mg/day were observed for the domains of language, visuospatial ability, and construction (MMSE 0 to 20). In the cohort of patients with more severe baseline disease (MMSE 0 to 16), significant clinical treatment benefits in favour of donepezil 23 mg/day were again evident in the domains of language, visuospatial ability, and construction, but also in the domains of memory and attention. Across both populations, scores declined with 10 mg on the domains of language, praxis, visuospatial ability, and construction, but scores on these domains were either improved or stabilized with 23 mg. Overall, most incremental benefits of treatment with donepezil 23 mg/day over 10 mg/day were seen in patients with more advanced baseline disease (MMSE 0 to 15).

These findings suggest that despite the advancing cholinergic deficit in AD, increasing levels of cholinesterase inhibition may help maintain certain cognitive abilities as the disease progresses. It may be the case that while patients with early-stage AD achieve sufficient response from lower-dose acetylcholinesterase inhibitors, patients with more advanced AD require higher doses to achieve an optimal response.

Another post hoc analysis using data from a large, 24-week, randomized, double-blind, international study enrolling patients with moderate to severe Alzheimer’s disease showed that the cognitive benefits of donepezil 23 mg/d over 10 mg/d were achieved regardless of the patient’s age, gender, weight, duration of prior donepezil 10 mg/d, and functional severity. The influence of baseline cognitive severity on response seemed to be dependent on the level of impairment, with cognitive benefits of donepezil 23 mg/d over 10 mg/d most apparent in those patients at a more advanced stage of disease.

**Dosage and administration**

A dose of 23 mg once daily can be administered once patients have been on a dose of 10 mg once daily for at least 3 months. The 23 mg tablet should not be split, crushed or chewed because this may increase its rate of absorption. It should be taken in the evening, just prior to retiring. It can be taken with or without food.

**Adverse reaction**

Studies showed that side effects were higher in patients receiving 23 mg/d (74%) than those receiving 10 mg/d (64%). The most common side effects in the 23-mg/d and 10-mg/d groups were nausea (12% vs. 3%, respectively), vomiting (9% vs. 3%), and diarrhoea (8% vs 5%). These gastrointestinal adverse effects were more frequent during the first month of treatment and were relatively infrequent beyond 1 month. Serious side effects, such as falls, urinary tract infection, pneumonia, syncope, aggression, and confusional state, were noted in a similar proportion of patients in the 23-mg/d and 10-mg/d groups; most of these were considered unrelated to treatment. So high-dose (23 mg/d) donepezil generally was well tolerated, with a typical AChEI safety profile but superior efficacy.
Conclusion

Because there are few FDA-approved treatments for AD, higher doses of donepezil may be an option for patients who have “maxed out” on their AD therapy or no longer respond to lower doses. Use of higher doses of donepezil may be a worthwhile goal to improve treatment of AD in patients with more advanced disease. The good safety and predictable tolerability profile for donepezil 23 mg/d supports its favorable risk/benefit ratio in patients with moderate to severe AD.

References