Buying Time: The Management of MCI and Early Dementia

Not all patients with MCI develop AD, but early AD often goes through a stage of MCI. In his presentation at the 12th Congress of the IPA, Dr. Stephen Salloway showed the benefit of treating patients with MCI or very mild AD with cholinesterase-inhibitor therapy.

Dr. Stephen Salloway, Director of Neurology and the Memory Disorders Program at Butler Hospital in Providence, Rhode Island, picked up where Dr. Nordberg left off, moving on to a critical evaluation of the use of cholinesterase inhibitors in the earliest stages of AD. He began by explaining that, while not all patients with MCI develop AD, the early course of AD is characterized by a period in which the patient may go through a stage of MCI (Figure 1).1 By the time the patient is diagnosed, the disease is most often well along its course.

Dr. Salloway stated that it is crucial to identify those patients with MCI most likely to progress to AD. He showed that several different subtypes of MCI have been identified, some of which are far more likely to progress to AD. Those with the amnestic subtype, he said, are those that merit the most consideration, while those with impairment in a single non-memory domain or in multiple domains are more likely to have other etiologies (Figure 2).2

The evidence supporting the position that amnestic MCI is likely to progress to AD includes a study that shows a significant prevalence of neuropsychiatric symptoms in MCI.3 These symptoms, Dr. Salloway showed, correlate well with those associated with mild AD (Table 1). As such, the presence of neuropsychiatric symptoms may be a major aid in identifying which patients with MCI will progress to AD.

One of these studies was a double-blind study conducted by Petersen et al in which the investigators evaluated subjects with the amnestic subtype of MCI.4 Dr. Salloway explained that the subjects in this study were randomized to receive 2000 IU of vitamin E daily, 10 mg of donepezil daily, or placebo for three years. The primary outcome of the study was transition to clinically possible or probable AD. The investigators also recorded cognition and functional assessments as secondary outcomes.

The study involved a total of 769 subjects. At baseline, the presence of the ApoE ε4 allele (which Dr. Salloway explained was a risk factor for the development of AD) was common (55% of the total cohort).

Results of this study showed that treatment with donepezil was associated with a reduced rate of conversion from MCI to probable or possible AD at six months and at one year. The difference was not, however, statistically significant for the rest of the study, out to three years (Figure 3).
Among the subgroup of amnestic MCI patients with the ApoE e4 allele, however, Dr. Salloway showed that the benefit of donepezil therapy appears to persist throughout the entire study period (Figure 4).

Recent trials testing the utility of other cholinesterase inhibitors in preventing the conversion from MCI to AD have also been completed. While he did not yet have the data for presentation, Dr. Salloway mentioned that other such studies were presented during the IPA Congress. One of these studies enrolled 1,018 patients with MCI and randomized them to treatment with rivastigmine or placebo for up to four years. The poster presentation for this study showed that of the 508 subjects randomized to rivastigmine, 17.3% converted to AD during the course of the study, compared to 21.4% of the 510 patients randomized to placebo. While this represented a 15% relative risk reduction, the effect was not statistically significant (p = 0.242).

Earlier studies had also evaluated donepezil in amnestic MCI. Dr. Salloway presented the results of such a study that he and his colleagues published in 2004. That study evaluated a total of 270 patients with MCI in a placebo-controlled, double-blind fashion over 24 weeks. Patients were randomized to receive donepezil (initially at 5 mg/day, titrated to 10 mg after 42 days) or placebo (n = 137).

Figure 2
Subtypes of MCI and Likely Etiologies

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Alzheimer’s disease</th>
<th>Vascular dementia</th>
<th>Lewy body dementia</th>
<th>Frontotemporal dementia</th>
<th>Primary progressive aphasia</th>
<th>Alzheimer’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild cognitive impairment</strong></td>
<td>Amnestic</td>
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<tr>
<td>Multiple domains slightly impaired</td>
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<tr>
<td>Single non-memory domain</td>
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The primary efficacy measures of the study were the New York University (NYU) Paragraph Delayed Recall test and the AD Cooperative Study Clinician’s Global Impression of Change for MCI (ADCS CGIC-MCI). A number of other secondary measures were also analyzed.

Dr. Salloway explained that there were no significant effects on the primary endpoints in the intention-to-treat analysis, but there were benefits in the recall test in the fully evaluable (FE) analysis.

More significant differences were shown in the secondary endpoints. In the modified AD Assessment Scale-Cognitive Subscale (ADAS-cog) analysis, for example, there were improvements in both groups, but those in the donepezil group were more robust (Figure 5). Tests of attention and psychomotor speed were also significantly better in donepezil-treated patients. Dr. Salloway also pointed out that adverse events, while more common in the donepezil group, were mild to moderate and transient.

Dr. Salloway also discussed the role of cholinesterase inhibition in patients a little further along in the AD spectrum—those with very mild AD. This portion of his presentation was based on a randomized, double-blind, placebo-controlled study in 153 patients with early-stage AD.

These patients received either donepezil (at 5 mg per day for the first six weeks, followed by 10 mg per day for an additional 18 weeks) or placebo. The primary efficacy measure was the ADAS-cog. Several other secondary endpoints were evaluated.

As shown in Figures 6 and 7, the investigators of this study detected improvements favoring donepezil on both the ADAS-cog and the MMSE. The differences were statistically significant in the former at 12 and 24 weeks and in the latter at six, 12 and 24 weeks.

Once again, Dr. Salloway showed that donepezil was safe and well tolerated in this population. Serious adverse events occurred in similar numbers of patients randomized to donepezil and placebo.

The overall efficacy and favorable tolerability of cholinesterase-inhibitor therapy in mild AD demonstrate that this intervention is desirable in this population. More studies are required in MCI, where findings suggest particular benefits in certain subgroups (e.g., those with amnestic MCI and the apoE ε4 allele) make it particularly important to develop strategies to determine the likelihood of MCI patients progressing to
AD and aggressively targeting these patients with cholinesterase-inhibitor therapy.

Dr. Salloway said that the evidence currently available suggests to him that "amnestic MCI is often prodromal AD and that there should be a discussion with patients about treatment [with cholinesterase inhibitors]."

References: