Tarenflurbil Slows Decline in Early AD

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

A drug that inhibits the formation of neurotoxic amyloid-β_{42} peptides slowed functional decline in patients with mild Alzheimer's disease by 46%, Dr. Gordon K. Wilcock and his colleagues have reported.

Patients who took the drug for 24 months fared significantly better than did those who switched to it after a year on placebo, prompting the investigators to conclude that tarenflurbil is truly a disease-modifying agent. "The randomized-start analysis suggests that, in patients with mild [Alzheimer's disease], treatment for 24 months resulted in greater benefit than did delayed treatment for 12 months," they wrote. "This smaller benefit in a delayed-start group is consistent with modification of the underlying disease process rather than a purely symptomatic effect" (Lancet Neurol. 2008;7:483-93).

Those patients who took the selective amyloid-lowering agent for 24 months fared far better than those who switched to it after a year on placebo.

Although tarenflurbil showed no significant functional or cognitive benefit for those with moderate disease, its benefit for early Alzheimer's disease (AD) patients raises hopes that an effective disease-modifying agent might be in the offing. A phase III trial of the drug was set to wrap up this spring, and the results are eagerly awaited, Dr. Paul Aisen of the University of California, San Diego wrote in an accompanying commentary (Lancet Neurol. 2008;7:468-9). "In a few months, we will learn whether tarenflurbil will be the first anti-amyloid strategy to be efficacious in a pivotal trial," wrote Dr. Aisen.

The study took place in 31 sites in Canada and the United Kingdom from November 2003 to April 2006. Dr. Wilcock of the University of Oxford, England, and his colleagues randomized 210 patients with mild to moderate Alzheimer's disease to one of three treatment regimens: tarenflurbil 400 mg twice daily, tarenflurbil 800 mg twice daily, or placebo.

After 12 months, 86 patients were included in a 12-month extension trial. In this study, patients taking the study drug continued on their respective regimens, while those taking placebo were randomized into the two active treatment arms.

Both trials included patients who had been stable on anticholinesterase drugs for at least 3 months prior to the study. All participants were assessed using the Alzheimer's Disease Assessment Scale, cognitive section (ADAS-cog), the Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL), and the Clinical Dementia Rating (CDR) sum of box score. The patients' mean age was 74 years; the mean Mini-Mental State Examination score was 21. About 95% were taking anticholinesterase drugs. Mild Alzheimer's was present in 130 patients at baseline, while the rest had moderate-stage disease.

Neither dosage of the study drug had any beneficial effect on patients with moderate AD, Dr. Wilcock and his coinvestigators said. In fact, after 12 months, those taking placebo actually fared better than those taking the higher dosage of tarenflurbil did. "In this group, treatment with placebo was associated with a significantly lower rate of decline in global function than was 800 mg tarenflurbil," the authors wrote.

Patients with mild disease responded much better to the drug. Compared with patients on placebo, those taking the 1,600-mg/day dosage experienced a 46% lower rate of decline on the ADCS-ADL and a 36% lower rate of decline on the CDR—both significant differences. While there was a trend toward a slower rate of cognitive decline (34% lower, compared with placebo), the difference did not reach statistical significance.

Global function was also assessed as an exploratory outcome measure with the clinician interview–based impression of change plus caregiver input. In this analysis, 31% of the patients taking the 1,600-mg/day dosage showed improved or unchanged function at 12 months, compared with only 19% of patients taking placebo.

After the initial 12-month study, 86 Canadian patients were enrolled in the 12-month extension study. Again, there were no significant beneficial effects in patients with moderate disease. However, compared with those on placebo, those taking 1,600 mg/day had significant slowing of decline in all three outcome measures: 44% less decline on the ADCS-ADL, 38% less decline on the CDR, and 61% less decline on the ADAS-cog.

There were five deaths in the first study; none was associated with the study drug.

Tarenflurbil is a selective amyloid-lowering agent (SALA). It works by changing the point at which the enzyme γ-secretase cleaves the amyloid-β protein. This prevents the formation of the toxic longer-chain amyloid-β_{42}. SALAs such as tarenflurbil are designed to reduce soluble amyloid-β levels, with the aim of preventing plaque formation.

The drug was previously named R-flurbiprofen. Results of the phase II trial were initially reported at the July 2006 International Conference on Alzheimer's Disease. Dr. Wilcock is a paid investigator for Myriad Pharmaceuticals, the Salt Lake City company that funded the study. ■

Progression From MCI to Dementia Affected by Gender

BY HEIDI SPLETE
Senior Writer

Risk factors for mild cognitive impairment and progression from mild cognitive impairment to dementia are not the same for men and women, findings from a population-based study of 6,892 adults aged 65 years and older show.

Identifying the risk factors that cause mild cognitive impairment (MCI) to progress to dementia can help determine which patients might benefit from treatment, Sylvaine Artero of the Institut National de la Santé et de la Recherche Médicale (INSERM) U888, Montpellier, France, and colleagues reported

Previous studies have addressed the risk factors for progression from MCI to Alzheimer's disease and dementia, but most of those have not involved a general population and have not addressed gender-specific factors.

To determine the gender-specific factors that predict progression of MCI to dementia, the investigators recruited 6,892 community-dwelling adults aged 65 years and older and followed them for 4 years. The average age of the participants was 74 years, and approximately half were women. The study was based on a large multicenter prospective study on brain aging sponsored in part by Sanofi-Synthelabo.

A total of 2,882 participants (42%) met the criteria for MCI at baseline. Over the next 4 years, 189 were diagnosed with dementia, 1,626 maintained a diagnosis of MCI, and 1,067 returned to a normal level of function (J. Neurol. Neurosurg. Psychiatry 2008 May 1 [doi:10.1136/jnnp.2007.136903]).

Overall, 8% of men with MCI developed dementia, compared with 6% of the women, but women were significantly less likely than men to return to normal cognitive function (36% vs. 39%) and significantly more likely to maintain a diagnosed cognitive disorder over the 4-year follow-up period (58% vs. 53%).

In a multivariate analysis, older age significantly predicted progression to dementia in men and women.

In men, progression from mild cognitive impairment to dementia was more than three times as likely if they had the apoE4 allele, and more than twice as likely in those with a history of stroke, a low level of education, or difficulty with daily activities as measured by the Instrumental Activities of Daily Living scale (IADL).

In women, progression from mild cognitive impairment to dementia was more than three times as likely if they had IADL deficits and more than twice as likely if they had the apoE4 allele, a low level of education, or subclinical depression. And the odds of progressing to dementia were almost twice as high in women who took anticholinergic inhibitors (odds ratio 1.8).

Significant predictors of progression from MCI to dementia in both men and women in a less rigorous, univariate analysis included the apoE4 genotype, hypertension, diabetes, age, a low level of education, low intelligence, subclinical depression, stroke, social isolation, and difficulty with at least one activity of daily living. "MCI cases in the general population can be differentiated by a much larger number of sociodemographic and clinical factors than previously observed," the investigators wrote.

The investigators said they had no financial conflicts to disclose. ■

Brain-Focused Regime Improves Gait Better Than Physical Therapy

WASHINGTON — An exercise program designed to overcome neural deficits improved elders' walking more than physical therapy that focused on lower-body muscles did, results of a randomized, controlled trial of the two approaches show.

Standard physical therapy aimed at building strength, flexibility, balance, and endurance has been shown to improve gait in older adults, but only modestly, said Jessie Van Swearingen, Ph.D., a physical therapist and rehabilitation specialist at the University of Pittsburgh. So she and her colleagues looked for an option.

"There is evidence that the brain has a significant impact on gait," she said while presenting the study at the annual meeting of the American Geriatrics Society. "We thought about motor learning because changes in gray-matter volume have been associated with slow speed and gait changes."

"Motor-learning" exercises involve goal-oriented stepping and walking, such as practicing stepping across and behind. Dr. Dr. Van Swearingen and her colleagues randomized 25 community-dwelling adults (average age 77 years) with gait problems to each of the interventions, which then took place in small group settings under the supervision of a physical therapist. Each group participated in 40- to 60-minute activity sessions twice a week for 12 weeks. Each session included 20-30 minutes of walking. Three people dropped out of the study for reasons unrelated to either intervention.

The motor-learning group practiced walking patterns including ovals, spirals, and serpentine paths. As the participants improved, they advanced to more-challenging walking patterns.

Participants in both groups showed improvements in gait abnormalities and walking speed during the study, but the motor-learning group's average improvements were significantly better than those of the standard group. Neither group reported a difference in perceived exertion after the interventions. Dr. Van Swearingen stated that she had no relevant financial conflict to disclose.

—Heidi Splete