

Rivastigmine Backed for Parkinson's Dementia

BY ELIZABETH MEHCATIE
Senior Writer

GAITHERSBURG, MD. — The cholinesterase inhibitor rivastigmine is likely to be approved for a second indication: the treatment of mild to moderate dementia associated with Parkinson's disease, based on a study that found treatment was associated with significant benefits in cognition, behavior, and activities of daily living in such patients.

Only one study of rivastigmine—the EXPRESS trial—has been submitted to the Food and Drug Administration for approval of the new indication. However, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee unanimously agreed that the study was well designed for evaluating the efficacy and safety of the drug in treating mild to moderate dementia associated with Parkinson's, the indication proposed for approval by the manufacturer, Novartis Pharmaceuticals. Usually two studies are submitted to the FDA for consideration for approving a drug.

The panel was not asked to specifically vote on whether to recommend approval, but all eight panelists at the meeting agreed that the overall data indicated that rivastigmine, at a dose of 3-12 mg per day, was safe in this population. The panel voted 7 to 0 with one abstention that, based on its results, the study did not need to be replicated for the FDA to approve the new indication.

"What convinces me that one study is enough" is the amount of safety data available for its use in Alzheimer's disease and "robust finding[s] on all secondary end points" for Parkinson's dementia, which were congruous with findings on the primary end points, said panel member Dr. Ralph L. Sacco, professor of neurology and epidemiology at the Neurological Institute of New York at Columbia University.

Novartis markets rivastigmine as Exelon, which was approved in the United States in 2000 for mild to moderate dementia of the Alzheimer's type. It was approved for the Parkinson's indication in the European Union earlier this year, but there are no treatments currently approved for this indication in the United States. The FDA usually follows the recommendations of its advisory panels.

The EXPRESS study compared the impact of rivastigmine with that of placebo over 24 weeks in 541 patients with mild to moderate dementia (362 on treatment, 179 on placebo) with a mean age of 72 years. They had been diagnosed with Parkinson's a mean of about 9 years earlier, and a mean of about 7 years had elapsed between their diagnosis and the appearance of the first dementia symptoms.

At 24 weeks, changes from baseline in the primary efficacy outcome end points, two subscales of the Alzheimer Disease Assessment Scale (ADAS) that assessed cognition and overall dementia, significantly favored those treated with rivastigmine. The secondary outcome measures of activities of daily living, executive function, attention, and behavior at 24 weeks were also signifi-

cantly improved among the treated patients.

Among those on rivastigmine, 27% discontinued treatment, compared with 18% of those in the placebo group; in both groups, most discontinued because of an adverse event. During the study and an extension study that followed patients for another 48 weeks, the most frequent side effects among treated patients were cholinergic, including nausea (29%), vomiting (17%), and worsening tremor (10%), which in most cases were mild to moderate and infrequently resulted in discontinuing treatment, according to Novartis.

Speaking on behalf of Novartis at the meeting, Dr. Clive Ballard, professor of age-related diseases at the Institute of Psychiatry, King's College, London, described Parkinson's dementia as a distinct dementia syndrome that can be "unambiguously diagnosed in routine clinical practice" by using three principles: The patient has an established diagnosis of idiopathic Parkinson's disease, develops dementia at least 1-2 years after the onset of PD, and has had other causes of dementia excluded.

Autopsy studies indicate that these criteria accurately diagnose 90% of cases, he said, adding that there is emerging evidence that a cholinergic deficit, shared by PD and Alzheimer's, is associated with many of the key cognitive deficits and neuropsychiatric symptoms.

In a unanimous vote, the panel agreed that there was a separate form of dementia associated with Parkinson's that is distinct from Alzheimer's disease, and that there are operational criteria that could be used for making the diagnosis clinically.

Dr. Russell Katz, director of the FDA's division of neurology products, explained that FDA reviewers had wanted to know whether the panel believed that the average practicing neurologist could reliably diagnose dementia in these patients and distinguish it from Alzheimer's dementia using the algorithm described by the company.

Panel member Dr. J. Eric Ahlskog, professor of neurology at the Mayo Clinic, Rochester, Minn., said that although clinicians in a busy clinic may not be good at sorting out specific changes such as changes in executive function, "we are pretty good as neurologists in saying yes, this person is demented." He agreed that the type of dementia could be ascertained by the two-step process of determining whether a patient has Parkinson's and whether he or she has developed dementia after an interval of time.

Panel member Dr. Irene Litvan, director of the movement disorders program at the University of Louisville (Kentucky), said she agreed that Parkinson's disease dementia is "a clear neurological entity."

While criteria for making the clinical diagnosis of dementia associated with Parkinson's are needed, Dr. Litvan, who is Raymond Lee Leiby professor of Parkinson's disease research at the university, said that for now, she "believe[s] that a neurologist will be able to apply the simple criteria and make a diagnosis of Parkinson's disease dementia and be able to treat it." ■

Poor Physical Function May Precede Dementia Onset

BY MARY ANN MOON
Contributing Writer

Older people with poor physical function are at higher risk for developing dementia than those with good physical function, reported Li Wang of the Veterans Affairs Puget Sound Health Care System, Seattle, and her associates.

In a study of 2,288 people aged 65 and older, patients with poor standing balance, slowed gait, and poor handgrip had an increased risk of cognitive impairment, dementia, or Alzheimer's disease (AD) developing during 6-year follow-up. The findings suggest physical decline may precede onset of dementia, which may in turn explain why other research has found that physical exercise appears to have a protective effect against dementia, the investigators said.

Ms. Wang and her associates used data from a population-based longitudinal study of aging to examine whether decline in motor function might be linked to progression to dementia. The study subjects were drawn from a random sample of patients enrolled in an HMO who were 65 or older from 1994 to 1996 (*Arch. Intern. Med.* 2006;166:1115-20).

All subjects had normal cognitive function on a battery of assessments at their initial screening. Attention, concentration, orientation, short-term memory, long-term memory, language ability, visual construction, list-generating fluency, abstraction, and judgment were assessed.

Subjects also underwent four physical performance tests: a 10-foot timed walk, timing of the interval required to rise from a seated position, standing balance, and grip strength. They were reexamined every 2 years to identify incident de-

mentia and AD, the investigators said.

During a 6-year follow-up, 1,422 subjects remained free of dementia, 362 died, 185 withdrew from the study, and 319 developed dementia—221 with AD, 55 with vascular dementia, and 43 with other types of dementia.

The incidence of dementia was 53/1,000 person-years for subjects who had poorer physical function at baseline (below the 25th percentile), compared with 17/1,000 person-years for those with better physical function.

Similarly, among subjects with the highest physical function scores at baseline, the incidence of dementia was 15/1,000 person-years, compared with an incidence of 58/1,000 person-years among those with lower scores.

When the results of each physical function test were considered separately, gait slowing and poor balance developed early, before any signs of cognitive impairment. Poor grip strength developed somewhat later, when cognitive impairment was just beginning to emerge.

"Gait and balance require integration of motor, sensory, and cerebellar activities, whereas grip requires a simpler motor activity. The more 'brain-challenging' tasks of gait and balance could be affected earlier in the course of dementia, whereas a simpler motor task such as grip would likely be preserved until later in the disease course," Ms. Wang and her associates said.

If their findings are confirmed in future studies, it would indicate that gait slowing and poor balance are earlier markers and poor handgrip a later marker of preclinical dementia, they added.

Until then, "we speculate that physical decline and cognitive decline may be inseparable during the development of dementia," they said. ■

More Physicians Needed to Meet Challenges of Aging Population

The number of new geriatricians in the United States is declining, even as the over-65 population grows rapidly, according to a report from the Center for Health Workforce Studies at the University at Albany, part of the State University of New York system.

The report, funded by the Health Resources and Services Administration, finds that although the projected number of physicians entering practice each year is expected to be adequate to meet the "aggregate demand," it may not be well matched to the needs of older Americans. In addition to the need for more geriatricians, the report points to the need for more mental health professionals, registered nurses, nursing home administrators, and other health care workers to meet the needs of the increasing older population.

The report also found that the de-

mand for services by older adults is likely to be affected by health insurance reimbursement policies, emerging technology, new models of care, and changes in the profession-specific scope of practice.

"The years between 2011 and 2050 will be the critical period for the U.S. health care system, as the baby boomers retire from the labor force," the report said. "It is not too early for the health care system to begin to prepare for those years, if it is to effectively meet the challenge of population aging."

The report details the broad impact of the aging population on the health care workforce and the impact on 18 specific health professions. The full report is available online at <http://chws.albany.edu>.

—Mary Ellen Schneider