Dopamine Agonists, L-Dopa Have Trade-Offs

BY DAMIAN McNAMARA

MIAMI BEACH — Levodopa produces greater symptomatic relief for Parkinson's disease patients compared with a dopamine agonist, consistent results of long-term studies indicate, but more dyskinesia and motor fluctuations are the trade-offs.

Dopamine agonists are still effective treatments for Parkinson's disease, said Dr. Cheryl Waters at World Federation of Neurology World Congress on Parkinson's Disease and Related Disorders. So how do you choose one or the other for initial therapy?

Use patient age as a general guide, she advised. Prescribe levodopa for older and dopamine agonists for younger patients. However, "we shouldn't be firmly stating use of a dopamine agonist or levodopa. We are individualizing therapy."

"The naysayers are going to say that … the long-term results of recent studies show people will ultimately do poorly," Dr. Waters said. "But we have a long course of Parkinson's disease. Let's look at that and not just focus on the end stages."

In the Comparison of the Agonist Pramipexole With Levodopa on Motor Complications of Parkinson's Disease, Dr. Waters, professor of clinical neurology at Columbia University Medical Center in New York City, and her colleagues randomized 151 patients to pramipexole and 150 others to levodopa in 1996 and 1997. The participants were permitted to switch to levodopa during an open-label phase. Six-year results for 222 participants showed that 50% of the initial pramipexole group and 69% of the initial levodopa group experienced motor complications (Arch. Neurol. 2009;66:563-70).

In addition, by the final visit, dyskinesias were more common in the initial levodopa group than in the initial pramipexole group (37% vs. 20%, respectively), she said. "Those in the pramipexole group have substantially remained on pramipexole all these years, even though they are not in the trial anymore," though the initial levodopa group reported less severe somnolence.

Clinical trials consistently show that dyskinesia is better with dopamine agonists while levodopa provides better symptomatic relief, but therapy should be individualized nonetheless.

Dr. Waters also referred to the Pergolide versus L-dopa monotherapy and positron emission tomography (PELMOPET) trial in which 148 early Parkinson's disease patients were randomized to pergolide (Permax) and another 146 to levodopa in this 3-year, multicenter, double-blind study (Mov. Disord. 2006;21:343-53).

There was a significant delay in the onset of dyskinesia and lower severity of motor symptoms in the pergolide group, Dr. Waters said. The levodopa group, however, reported significantly greater symptomatic relief on the Unified Parkinson's Disease Rating Scale (UPDRS) sections I, II, and III; Clinical Global Impressions severity and improvement ratings; and the Patient Global Impressions improvement scale.

The authors concluded from these results that both agents are suitable for initial therapy. However, pergolide was withdrawn from the U.S. market in 2007 because of its potential for causing heart valve damage.

Dr. Waters also addressed the 10-year results of a ropinirole (Requip) versus levodopa study (Mov. Disord. 2007;22:2409-17).

This was an extension of a study that compared treatment with ropinirole in 85 patients with levodopa therapy in 45 patients at 5 years (N. Engl. J. Med. 2000;342:1484-91). At that time point, the cumulative incidence of dyskinesia was 20% with ropinirole, compared with 45% with levodopa.

At 10 years, 51 patients remained in the ropinirole cohort and 29 in the levodopa group. "The numbers were small. Not all centers participated," Dr. Waters said. "Even after the 10 years, there was a substantial difference in those being free of dyskinesia for those initially randomized to ropinirole [52%] versus levodopa [77%]."

"These clinical trials are all quite consistent," Dr. Waters said. "Dyskinesia is better with dopamine agonists and the [symptomatic] effect of levodopa is greater." ■

Latrepirdine Improved Cognitive Symptoms in Huntington's

BY JEFF EVANS

Cognitive impairment improved in patients with mild to moderate Huntington's disease without any noticeable increase in adverse events after a 90-day course of treatment with the investigational drug latrepirdine.

The drug, known most widely outside of the United States under the trade name Dimebon, was well tolerated in the trial and showed no signs of increasing the risk for particular adverse events, reported Dr. Karl Kieburtz of the University of Rochester (N.Y.), and his colleagues in the Dimebon in Subjects With Huntington Disease (DIMOND) study (Arch. Neurol. 2010;67:154-60).

VITALS

Major Finding: Latrepirdine was well tolerated, had low adverse event rates, and significantly improved MMSE scores by 1 point over 90 days.

Data Source: Randomized, placebo-controlled, phase II trial of 90 patients with mild to moderate Huntington's disease

Disclosures: Some investigators are employees of Medivation Inc., which manufactures latrepirdine and sponsored the study sponsor; others reported receiving prior research support from the company.

Latrepirdine is a synthetic molecule that is known to stabilize mitochondrial membranes and increase neurite outgrowth. It is currently also being tested in phase III trials of patients with Alzheimer's disease.

The patients had a mean age of about 53 years and had to be ambulatory, have a total functional capacity score of 5 or higher at baseline on the Unified Huntington Disease Rating Scale (UHDRS), and be living in the community without requiring skilled nursing care.

After starting latrepirdine at 10 mg/day on day 1 and then 30 mg/day for the following 6 days, the dose was titrated up to 60 mg/day after the first week. The study, comprising 90 subjects, was completed by 87% of patients in the latrepirdine group and by 82% on placebo.

In the trial, all efficacy outcomes were secondary end points. On the Mini-Mental State Examination (MMSE), 46 latrepirdine-treated patients had a mean improvement of nearly 1 point on the MMSE, compared with no change in 44 placebo-treated patients. No significant differences in outcomes could be detected between the groups on other measures of cognitive function, such as the Alzheimer's Disease Assessment Scale–Cognitive subscale or the cognitive tests in the UHDRS.

Dr. Kieburtz and his associates thought that the "significant finding on the MMSE was surprising, given that the [examination] is generally considered a relatively insensitive measure of cognitive function."

However, the researchers noted that the "MMSE provides a broader assessment of cognition than the other end points assessed" and "it is highly stable during a 6-month to 12-month period with low variability in patients who were untreated."

A "substantial number" of patients in both groups had maximum or near-maximum scores on the MMSE at baseline. To determine the effect of latrepirdine in patients with more severe cognitive impairment, the investigators analyzed the outcomes for 51 patients with an MMSE score of 26 or lower. At 90 days, the mean MMSE score of patients in this subgroup who received latrepirdine was 1.63 points greater than the score of those who received placebo.

Adverse events occurred in similar percentages of patients treated with latrepirdine (70%) or placebo (80%); about half of these were moderate to severe in intensity. The only adverse events that occurred more often in latrepirdine-treated patients than in placebo-treated patients were headache (15% vs. 7%, respectively) and somnolence (7% vs. 2%). ■

MY TAKE

Stage Set for Future Trials

This effort by Dr. Kieburtz and his colleagues is noteworthy for a number of reasons. Although Xenazine (tetrabenazine) is approved for the treatment of chorea and other motor manifestations of HD, there are no approved medications available for cognitive and behavioral symptoms in the disease.

Dr. Kieburtz presents data on the safety and tolerability of latrepirdine given 20 mg three times daily compared with placebo in patients diagnosed with HD. The treatment and placebo groups were similar and randomization methods were strict.

Although the study was not designed to detect a minimally clinically significant effect on any efficacy measure, a small positive change observed in MMSE testing suggests that further study with this agent is warranted. The unique proposed mechanism of action of latrepirdine to stabilize mitochondrial membranes distinguishes it from medications commonly used in HD such as anticholinesterase inhibitors and *N*-methyl-D-aspartate antagonists, giving hope for a new avenue of therapeutic intervention in this challenging neurodegenerative disorder.

The investigators' carefully designed and executed work sets the stage for future treatment trials focused on cognitive and behavioral efficacy in HD.

DR. BENN E. SMITH *is director of the electromyography and sensory laboratories at the Mayo Clinic Arizona. He has no relevant disclosures.*