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Pimavanserin reduced dementia-related psychotic symptoms without affecting cognition

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REPORTING FROM CTAD 2019

SAN DIEGO – Pimavanserin, a second-generation antipsychotic approved for hallucinations and delusions in patients with Parkinson's disease, may also be helpful for psychotic symptoms in other dementia patients, Erin P. Foff, MD, said at the Clinical Trials on Alzheimer's Diseaseconference.

Michele G. Sullivan/MDedge News

Dr. Erin P. Foff

In fact, the phase 3 HARMONY trialwas stopped early, after an interim efficacy analysis determined that treatment with pimavanserin (Nuplazid) had achieved its primary endpoint – a statistically significant threefold reduction in the risk of relapse (*P* less than .0033).

Importantly, pimavanserin didn't significantly affect cognition nor, at least in this controlled setting, did it appear to increase falls or other adverse events often seen with antipsychotic use in elderly patients, said Dr. Foff, clinical lead for the dementia-related psychosis program at Acadia Pharmaceuticals, which makes the drug and sponsored the study.

Based on the positive results, Acadia intends to submit a supplemental new drug application for this indication, according to an investor presentationposted on the company website.

"There is a critical need for an intervention [for psychosis symptoms] in this population," Dr. Foff said. "We saw a robust response that was well tolerated and well maintained with no negative impact on cognitive scores."

The second-generation antipsychotic was approvedin 2016 for treating hallucinations and delusions in patients with Parkinson's disease.

The drug is a selective antagonist of 5-HT_2 receptors, with low affinity for dopamine receptors. This slightly differentiates it from other second-generation antipsychotics that affect dopamine receptors as well as 5-HT_2 receptors.

HARMONY was not a typical placebo-controlled, randomized efficacy trial. Rather, it employed a two-phase design: an open-label treatment response period followed by a placebo-controlled randomization limited to open-label responders. Overall, HARMONY involved 392 patients with mild to severe dementia of numerous etiologies, including Alzheimer's disease (66.8%), Parkinson's disease dementia (14.3%), frontotemporal dementia (1.8%), vascular dementia (9.7%), and dementia with Lewy bodies (7.4%). All patients entered a 12-week, open-label period during which they received pimavanserin 34 mg daily. The primary endpoint was a combination of least a 30% reduction on the total Scale for the Assessment of Positive Symptom–Hallucinations and Delusions (SAPS-HD) scale plus a score of 1-2 on the Clinical Global Impressions–Improvement (CGI-I) scale, meaning better or very much better.

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At 12 weeks, all responders were then randomized to placebo or continued therapy for 26 weeks. The primary endpoint was relapse, defined as at least a 30% worsening of the SAPS-HD relative to open-label baseline, plus a CGI-I score of 6-7 (worse or very much worse).

Patients were aged a mean of 74 years. Most (about 90%) were living at home. Visual hallucinations occurred in 80% and delusions in 83%. At baseline, the mean SAPS-HD score was 24.4, and the mean CGI-Severity score was 4.7. The mean Mini-Mental State Exam (MMSE) score was 16.7.

In the open-label period, pimavanserin reduced the SAPS-HD score at 12 weeks by a mean of 75%. Symptoms began to decline in the first week of treatment, with continuing improvement throughout the treatment period. By week 4, 30% had hit the response

target. This number increased steadily, with 51% responding by week 4, 75% by week 8, and 88% by week 12.

By probable diagnosis, response rates were 59.8% in Alzheimer's patients, 45.5% for those with Lewy body dementia, 71.2% among patients with Parkinson's disease, 71% in patients with vascular dementia, and 50% in patients with frontotemporal dementia. In the final analysis, 80% of patients overall were considered responders.

The randomized potion began immediately thereafter with no washout period. About 62% (194) of the entire cohort – all responders – entered into the placebo-controlled phase. The remaining patients were either not responders (20%), dropped out because of an adverse event (7.7%), or left the study for unspecified reasons (10%). There was one death, which was not related to the study medication. A total of 41 patients were still being treated when the study was discontinued, and they were excluded from the final analysis.

When the randomized study ended, relapses had occurred in 28.3% of those taking placebo and in 12.6% of those taking pimavanserin – a statistically significant difference (hazard ratio, 0.353). This translated to a 180% reduction in relapse.

The rate of adverse events was similar in both active and placebo groups (41% vs. 36.6%). Serious adverse events occurred in 4.8% and 3.6%, respectively. The most commonly reported adverse events were headache (9.5% vs. 4.5%) and urinary tract infection (6.7% vs. 3.6%). Asthenia occurred in 2.9% of treated patients and 0.9% of placebo patients, but no falls were reported. Anxiety and dizziness were also reported in three patients taking the study medication.

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Three patients (2.9%) experienced a prolonged QT phase on ECG, with a mean delay of 5.4 milliseconds from baseline. "Pimavanserin is known to have this effect of QT prolongation," Dr. Foff said. "This 5.4-ms change is exactly in line with what we already know about pimavanserin and is not clinically significant. We saw no effect on motor function, consistent with the mechanism of action, and very low levels of agitation or aggression."

Pimavanserin didn't significantly change cognition from baseline in the open-label period, and in the randomized period, MMSE never differed significantly between groups.

The company also conducted an exploratory subgroup analysis that looked at placebo versus pimavanserin relapse by probable clinical diagnosis. Among the types of dementia, relapse rates for placebo versus pimavanserin were 23% versus 13% among Alzheimer's patients, 67% versus 0% in Lewy body dementia patients, 50% versus 7% in patients with Parkinson's, and 17% each among vascular dementia patients. Only one patient in the randomized period had frontotemporal dementia, and that patient relapsed on treatment.

Whether pimavanserin is effective specifically for psychosis in Alzheimer's disease patients, however, remains in question. In 2018, Acadia published a negative phase 2 trialin a targeted group of 181 Alzheimer's patients. The primary outcome in each study was mean change on the Neuropsychiatric Inventory–Nursing Home Version psychosis score (NPI-NH-PS). Clive Ballard, MD, of the University of Exeter (England), was the primary investigator.

After 6 weeks, those taking pimavanserin had a 3.76-point change in the NPI-NH-PS, compared with a 1.93-point change in the placebo group. The mean 1.84-point difference was not statistically significant.

This Alzheimer's-only cohort group also experienced more adverse events than the HARMONY mixed-diagnosis cohort did, although the differences between pimavanserin and placebo groups were not significant. Adverse events included falls (23% of each group) and agitation (21% with pimavanserin vs. 14% with placebo). Cognition was unaffected.

Later that year, Acadia published a subgroup analysisof the same cohort parsing response by symptom severity, again with Dr. Ballard as the lead investigator.

The analysis focused on 57 patients with a baseline NPI-NH-PS of at least 12, indicating severe symptoms of psychosis.

Treatment effects were more pronounced in this group, significantly favoring pimavanserin. On the NPI-NH-PS, 88.9% of the pimavanserin group and 43.3% of the placebo group had at least a 30% improvement; 77.8% and 43.3% experienced at least a 50% improvement. The rate of serious adverse events was similar (18% with pimavanserin and 17% with placebo) and cognition was unaffected. Falls occurred in 14% of the treated group and 20% of the placebo group.

"These findings coupled with the results from other studies of pimavanserin suggest a potential role for pimavanserin in treating psychosis in patients across a range of neuropsychiatric conditions," Dr. Ballard wrote.

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