Lacosamide Shows Epilepsy Efficacy in Phase III

BY MITCHEL L. ZOLER
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PHILADELPHIA — Lacosamide, a new antiepileptic drug, showed safety and efficacy in a total of about 1,300 patients when used as an adjunctive agent for patients who failed treatment with one or more of the second-generation antiepileptic drugs, judging from findings from three phase III trials.

"If you look at the efficacy trials for the new antiepileptic drugs [now on the market], such as levetiracetam and lamotrigine, the patients they were tested on had failed treatment with older drugs, like carbamazepine, phenytoin, and valproic acid. In the lacosamide trials, the patients often failed on the drugs that are more commonly used today, the second-generation drugs," Dr. Steve S. Chung said while presenting a poster at the annual meeting of the American Epilepsy Society. "Patients who failed on newer drugs [such as oxcarbazepine, levetiracetam, and lamotrigine] still had a very significant response to lacosamide."

If lacosamide comes onto the U.S. market, it could be used as a second-line agent for patients who fail one or more newer drugs, said Dr. Chung, director of the epilepsy monitoring unit at the Barrow Neurological Institute, Phoenix. "I don't see using lacosamide as a first-line agent anytime soon," he added.

Schwarz Pharma AG, a division of UCB SA, which is developing lacosamide (Vimpat), filed a New Drug Application with the Food and Drug Administration last September, and the company expects a decision by the agency by July 2008. Two indications were included in the application: the treatment of partial-onset seizures in adults with epilepsy, and the treatment of neuropathic pain in patients with diabetes. Dr. Chung received research support from and is a speaker for UCB and Schwarz.

The study that he led randomized 405 patients with simple or complex partial seizure to treatment with 400 mg or 600 mg of oral lacosamide or placebo daily. Patients were escalated to their target dosages by 100-mg/day increments weekly during an escalation phase that lasted up to 6 weeks. They were then maintained on treatment with their study medication as well as their background regimen for 12 weeks, when efficacy was assessed.

During maintenance treatment, the 204 patients on the 400-mg/day regimen had an average drop of 36% in their seizure recurrence rate.

The most common antiepileptic drugs that the patients were on when they entered the trial were levetiracetam (Keppra) in 40%; lamotrigine (Lamictal) in 36%; carbamazepine (Tegretol), 25%; oxcarbazepine (Trileptal), 21%; phenytoin (Dilantin), 19%; topiramate (Topamax), 18%; and valproic acid (Depakote), 17%. (The total is greater than 100% because many patients were taking more than one drug.)

During maintenance treatment, the 204 patients on the 400-mg/day regimen and the 97 patients on the 600-mg/day regimen had an average drop in their seizure recurrence rate of 36% and 37%, respectively, compared with baseline. The 104 placebo patients had an average 21% reduction in seizures. The difference between the placebo group and each of the drug-treated groups was statistically significant.

Both lacosamide regimens also led to significant boosts in the percentage of patients who had a 50% or greater drop in their seizure frequency.

The magnitude of the drug's effect, compared with placebo, is similar to what had been previously shown for other second-generation antiepileptic drugs, such as levetiracetam and lamotrigine, Dr. Chung said in an interview.

The safety analysis showed that lacosamide treatment, compared with placebo, was associated with an increase in the incidence of certain adverse events, especially during the dose-escalation phase of the study. Most events were mild or moderate in intensity.

The most common adverse event was dizziness, which occurred during the dose-escalation phase in 37% of the patients treated with 400 mg/day and in 43% of those receiving 600 mg/day, compared with a 9% rate in the placebo patients. During the maintenance phase, dizziness was reported by 8% of patients receiving 400 mg/day, by 1% of those getting 600 mg/day, and by 2% of the placebo patients.

Other adverse events during the dose-escalation phase included nausea, diplopia, blurred vision, vomiting, headache, and tremor. Each of these occurred in 6%-19% of patients, compared with rates of 1%-7% in the placebo patients.

During the maintenance phase, all of these adverse events occurred in 1%-11% of patients treated with lacosamide, compared with rates of 1%-7% in the placebo patients.

Because the adverse events linked to lacosamide appeared to be greatest during the dose-escalation phase, it may help to introduce the drug more slowly, using 50-mg/day increments instead of 100-mg/day increases, and stretching out the dose-escalation phase for a longer period of time, Dr. Chung said. The target therapeutic dosage should be 400 mg/day because it seemed to have similar efficacy to the higher dosage while causing somewhat fewer adverse events, he said.

The two other phase III trials that produced the additional data submitted to the FDA were done in Europe. One study used lacosamide dosages of 200 mg, 400 mg, or 600 mg/day, as well as placebo, and involved 418 patients. The second study used lacosamide dosages of 200 mg or 400 mg/day and placebo, and involved 485 patients. Both studies had results that were similar to those reported by Dr. Chung. The 200-mg/day dosage was significantly less effective than the higher dosages.

Lacosamide has a unique mechanism of action compared with other antiepileptic drugs. The drug's effect appears due to its inhibition of the slow phase of sodium-channel inactivation. When certain neurons are stimulated, their sodium channels are activated, and then they become inactive again. The inactivation process involves both a fast phase and slow phase. By inhibiting the slow-phase of inactivation, treatment with lacosamide prolongs the activation of sodium channels in neurons.

Lacosamide also suppresses axon regeneration. This effect is believed to be responsible for the drug's activity in reducing diabetic neuropathy. When axons are damaged by diabetic neuropathy, the neurons often regenerate, but in an abnormal way that leads to pain. Treatment with lacosamide appears to inhibit axonal regrowth, Dr. Chung said. ■

Drug Withdrawal Safe After a Prolonged Seizure-Free Period

BY MITCHEL L. ZOLER
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PHILADELPHIA — Most epilepsy patients whose seizures are completely controlled by antiepileptic drugs can eventually attempt withdrawal from treatment with a low risk of complications, Dr. Peter Camfield said at the annual meeting of the American Epilepsy Society.

The major nightmare of stopping antiepileptic therapy—that after successful drug treatment is stopped seizures will recur and will no longer be controllable by medications—occurs infrequently, and so attempting to take patients off of their drugs is a reasonable option for most epilepsy patients, said Dr. Camfield, a pediatric neurologist and head of the pediatrics division at Dalhousie University in Halifax, N.S.

In fact, "most children deserve a chance to come off of their AEDs [antiepileptic drugs] after being seizure free for 1-2 years," he said. About 70% of children with epilepsy who are treated with AEDs become seizure free long enough to become candidates for discontinuation.

He cited data from the Nova Scotia follow-up study, which included 692 children with epilepsy; 389 patients were seizure free after treatment for at least 2 years and so were eligible to stop treatment. From this group, 280 patients elected to do so. Among those who stopped, 81 (29%) had a recurrence of seizures; the remaining 71% of patients remained seizure free without treatment during long-term follow-up.

Of the 81 children who had a recurrence, 78 (96%) were controlled again by restarting AED treatment. Only three patients were intractable to restarted treatment, less than 1% of the 389 who were eligible to try discontinuation, Dr. Camfield said.

A much lower percentage of adults are willing to stop their AEDs, and so the available data on adults are more limited. A literature review published in 2005 indicated that if seizures recur after treatment is stopped, about 80% of adult patients can quickly have their seizures controlled again by restarting treatment. The percentage of adults with seizures that are refractory to restarted treatment is low, but the rate may be higher than it is in children. It's reasonable to consider stopping AED treatment in adults who have been seizure free for about 4 years, Dr. Camfield said.

Stopping a successful AED regimen is a decision that patients—or their families—need to make individually, using the information that's available. Stopping treatment has the advantages of avoiding AED adverse effects and giving patients a sense that they are cured. Disadvantages include interrupting successful management; risking an unexpected recurrence that could have serious consequences, such as a seizure when driving, and concern about the rare case in which restarting treatment is not successful. Patients should also understand that even if they continue a successful regimen, there is no guarantee that they will remain seizure free in the future.

Childhood epilepsy syndromes can be classified by how often they remit. About 15% of patients always remit: those with benign rolandic seizures, benign familial infantile seizures, and early-onset, benign occipital epilepsy.

About 75% of children with epilepsy—a group that includes 17 different syndromes—will sometimes remit. Among these are typical childhood absence epilepsy, with about a 65% remission rate; cryptogenic partial epilepsy, with a 67% remission rate; and symptomatic partial seizures, with about a 50% remission rate.

About 10% of children with epilepsy never remit, including patients with juvenile myoclonic epilepsy, reading epilepsy, myoclonic absence epilepsy, and early myoclonic encephalopathy.

Although Dr. Camfield recommended that seizure-free patients wait 2 years (for children) to 4 years (for adults) before attempting to stop their treatment, results from observational studies suggest that children have about the same recurrence risk following drug discontinuation regardless of whether it occurs after 1, 2, 3, 4, or 5 years of seizure-free treatment. The data suggest that "AED treatment has nothing to do with remission of epilepsy," he said.

In a Dalhousie University study, the significant predictors for the risk of recurrence in children following treatment withdrawal were female gender, an abnormal neurologic examination, epilepsy onset before the age of 10 years, and having a history of focal seizures (which was the strongest risk factor). The risk of recurrence was even higher in patients who had two or more of these risk factors. ■