Valproate Doesn't Delay Psychosis in Alzheimer's

BY MICHELE G. SULLIVAN

VIENNA — Valproate treatment over 2 years does nothing to delay the onset of agitation or psychosis in patients with Alzheimer's disease, and patients taking the anticonvulsant showed significantly more brain volume loss on MRI at year 1 than did those taking placebo, based on the results of a randomized trial.

But because the changes in brain volume did not correlate with any clinical differences between the groups, it's difficult to know just what to make of the observed volume loss, Dr. Pierre Tariot said at the International Conference on Alzheimer's Disease.

"Interpretation of these results really isn't possible at this juncture," said Dr. Tariot of the Banner Alzheimer's Institute, Phoenix, in an interview. "It could theoretically represent damage to the brain, but that seems unlikely due to the absence of correlation with clinical decline that is seen in natural history studies. There are case reports of 'pseudoatrophy' associated with valproate use, which may be relevant here. We have an ongoing analysis, and the full details will be presented at a later time."

The trial randomized 313 patients with mild-moderate Alzheimer's disease who lacked agitation or psychosis at baseline to either placebo or an extended-release form of divalproex sodium (Depakote ER) at a dose of 10-12 mg/kg per day. The primary outcome was time until the emergence of agitation and/or psychosis. The symptoms had to last at least 2 weeks, and had to be clinically significant in the opinion of the site physician.

MRI of the brain was performed on a subset of 90 patients at baseline and 1 year.

The patients' mean age was 75 years; their mean Mini Mental State Exam at baseline was 17 and the mean Neuropsychiatric Inventory score was 3. Most of the patients (70%) were positive for the high-risk apolipoprotein E e4 allele.

There were no between-group differences in time to agitation or psychosis. In fact, although the study assumed an incidence of 50% by the end of the trial, only 17% of the entire cohort developed either of these symptoms, said Dr. Tariot, who received consulting fees and research funding from Abbott Laboratories, which manufactures Depakote ER. Abbott supplied the drugs for the trial and funded the MRI portion of the trial.

Valproate appeared to reduce brain volume, but this difference did not correlate with clinical outcomes.

DR. TARIOT

There also were no between-group differences in any of the secondary end points, confirming that valproate confers no clinically discernible neuroprotective benefit. Patients taking placebo had a slightly better score on the Alzheimer's Disease Cooperative Study activities of daily living at 24 months, Dr. Tariot said, but that difference did not reach significance after adjustment for multiple comparisons.

Consistent with known effects of the medication, patients taking valproate had significantly more central nervous system side effects (gait disturbance, tremor, and sedation), and gastrointestinal side effects (abdominal pain, loose stool).

In the MRI substudy, total brain volume and bilateral hippocampal volume were significantly decreased in the valproate group, compared with placebo, while ventricular volume was significantly increased in the active treatment group, compared with the placebo group. However, Dr. Tariot noted, there were no differences in clinical outcomes between these two subgroups.

The conference was sponsored by the Alzheimer's Association. ■

In all controlled and uncontrolled trials in patients with partial-onset seizures, 1327 patients have received VIMPAT of whom 1000 have been treated for longer than 6 months and 852 for longer than 12 months.

Clinical Trials Experience

Controlled Trials

Adverse reactions leading to discontinuation

In controlled clinical trials, the rate of discontinuation as a result of an adverse event was 8% and 17% in patients randomized to receive VIMPAT at the recommended doses of 200 and 400 mg/day, respectively, 29% at 600 mg/day, and 5% in patients randomized to receive placebo. The adverse events most commonly (>1% in the VIMPAT total group and greater than placebo) leading to discontinuation were dizziness, ataxia, vomiting, diplopia, nausea, vertigo, and vision blurred.

Most common adverse reactions

Table 2 gives the incidence of treatment-emergent adverse events that occurred in ≥2% of adult patients with partial-onset seizures in the total VIMPAT group and for which the incidence was greater than placebo. The majority of adverse events in the VIMPAT patients were reported with a maximum intensity of 'mild' or 'moderate'.

Table 2: Treatment-Emergent Adverse Event Incidence in Double-Blind, Placebo-Controlled Partial-Onset Seizure Trials (Events ≥2% of Patients in VIMPAT Total and More Frequent Than in the Placebo Group)

System Organ Class/ Preferred Term	Placebo N=364 %	VIMPAT 200 mg/day N=270 %	VIMPAT 400 mg/day N=471 %	VIMPAT 600 mg/day N=203 %	VIMPAT TOTAL N=944 %
Ear and labyrinth disorder					
Vertigo	1	5	3	4	4
Eye disorders					
Diplopia	2	6	10	16	11
Vision blurred	3	2	9	16	8
Gastrointestinal disorders					
Nausea	4	7	11	17	11
Vomiting	3	6	9	16	9
Diarrhea	3	3	5	4	4
General disorders and administration site conditions					
Fatigue	6	7	7	15	9
Gait disturbance	<1	<1	2	4	2
Asthenia	1	2	2	4	2
Injury, poisoning and procedural complications					
Contusion	3	3	4	2	3
Skin laceration	2	2	3	3	3
Nervous system disorders					
Dizziness	8	16	30	53	31
Headache	9	11	14	12	13
Ataxia	2	4	7	15	8
Somnolence	5	5	8	8	7
Tremor	4	4	6	12	7
Nystagmus	4	2	5	10	5
Balance disorder	0	1	5	6	4
Memory impairment	2	1	2	6	2
Psychiatric disorders					
Depression	1	2	2	2	2
Skin and subcutaneous disorders					
Pruritus	1	3	2	3	2

Laboratory abnormalities

Abnormalities in liver function tests have been observed in controlled trials with VIMPAT in adult patients with partial-onset seizures who were taking 1 to 3 concomitant anti-epileptic drugs. Elevations of ALT to ≥3× ULN occurred in 0.7% (7/935) of VIMPAT patients and 0% (0/356) of placebo patients**.** One case of hepatitis with transaminases >20x ULN was observed in one healthy subject 10 days after VIMPAT treatment completion, along with nephritis (proteinuria and urine casts). Serologic studies were negative for viral hepatitis. Transaminases returned to normal within one month without specific treatment. At the time of this event, bilirubin was normal. The hepatitis/nephritis was interpreted as a delayed hypersensitivity reaction to VIMPAT.

Other Adverse Reactions in Patients with Partial-Onset Seizures

The following is a list of treatment-emergent adverse events reported by patients treated with VIMPAT in all clinical trials in patients with partial-onset seizures, including controlled trials and long-term open-label extension trials. Events addressed in other tables or sections are not listed here. Events included in this list from the controlled trials occurred more frequently on drug than on placebo and were based on consideration of VIMPAT pharmacology, frequency above that expected in the population, seriousness, and likelihood of a relationship to VIMPAT. Events are further classified within system organ class.

Blood and lymphatic system disorders: neutropenia, anemia

Cardiac disorders: palpitations

Ear and labyrinth disorders: tinnitus

Gastrointestinal disorders: constipation, dyspepsia, dry mouth, oral hypoaesthesia

General disorders and administration site conditions: irritability, pyrexia, feeling drunk

Injury, poisoning, and procedural complications: fall

Musculoskeletal and connective tissue disorders: muscle spasms

Nervous system disorders: paresthesia, cognitive disorder, hypoaesthesia, dysarthria, disturbance in attention, cerebellar syndrome

Psychiatric disorders: confusional state, mood altered, depressed mood

Intravenous Adverse Reactions

Adverse reactions with intravenous administration generally appeared similar to those observed with the oral formulation, although intravenous administration was associated with local adverse events such as injection site pain or discomfort (2.5%), irritation (1%), and erythema (0.5%). One case of profound bradycardia (26 bpm: BP 100/60 mmHg) was observed in a patient during a 15 minute infusion of 150mg VIMPAT. This patient was on a beta-blocker. Infusion was discontinued and the patient experienced a rapid recovery.

Comparison of Gender and Race

The overall adverse event rate was similar in male and female patients. Although there were few non-Caucasian patients, no differences in the incidences of adverse events compared to Caucasian patients were observed.

DRUG INTERACTIONS

Drug-drug interaction studies in healthy subjects showed no pharmacokinetic interactions between VIMPAT and carbamazepine, valproate, digoxin, metformin, omeprazole, or an oral contraceptive containing ethinylestradiol and levonorgestrel. There was no evidence for any relevant drug-drug interaction of VIMPAT with common AEDs in the placebo-controlled clinical trials in patients with partial-onset seizures [see *Clinical Pharmacology (12.3)* in Full Prescribing Information)].

The lack of pharmacokinetic interaction does not rule out the possibility of pharmacodynamic interactions, particularly among drugs that affect the heart conduction system.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

Lacosamide produced developmental toxicity (increased embryofetal and perinatal mortality, growth deficit) in rats following administration during pregnancy. Developmental neurotoxicity was observed in rats following administration during a period of postnatal development corresponding to the third trimester of human pregnancy. These effects were observed at doses associated with clinically relevant plasma exposures.

Lacosamide has been shown *in vitro* to interfere with the activity of collapsin response mediator protein-2 (CRMP-2), a protein involved in neuronal differentiation and control of axonal outgrowth. Potential adverse effects on CNS development can not be ruled out.

There are no adequate and well-controlled studies in pregnant women. VIMPAT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Oral administration of lacosamide to pregnant rats (20, 75, or 200 mg/kg/day) and rabbits (6.25, 12.5, or 25 mg/kg/day) during the period of organogenesis did not produce any teratogenic effects. However, the maximum doses evaluated were limited by maternal toxicity in both species and embryofetal death in rats. These doses were associated with maternal plasma lacosamide exposures [area under the plasma-time concentration curve; (AUC)] ≈2 and 1 times (rat and rabbit, respectively) that in