

Androgen Reduction Has Few Benefits for SBMA

VITALS

Major Finding: Men with spinal and bulbar muscular atrophy who were treated with dutasteride for 2 years had significantly better physical quality of life, but significantly worse mental quality of life, than did placebo-treated patients. No differences in muscle strength were found.

Data Source: A phase II, randomized, double-blind, placebo-controlled trial of 50 men

Disclosures: The trial was funded by the National Institute of Neurological Diseases and Stroke. None of the investigators had relevant disclosures.

BY JEFF EVANS

BALTIMORE — Long-term dutasteride therapy in men with spinal and bulbar muscular atrophy does not appear to improve muscle strength or fatigue and might actually lower mental quality of life, according to the results of a phase II, randomized, double-blind, placebo-controlled trial.

Patients derived some benefit from treatment with the 5-alpha reductase inhibitor, which converts testosterone into more potent dihydro-

testosterone, as a result of a significant reduction in their number of falls and improvement in their physical quality of life.

Spinal and bulbar muscular atrophy (SBMA) is characterized by a toxic buildup of mutant androgen receptors with an excessively long string of glutamine residues in motor neurons. This buildup weakens bulbar and extremity muscles, causing difficulty with gait and dysphagia, and also might lead to gynecomastia, infertility, and other manifestations of androgen insensitivity. Dutasteride has

VIMPAT® (lacosamide) Tablets, CV VIMPAT® (lacosamide) Injection, CV Brief Summary of Full Prescribing Information (See Package Insert for Full Prescribing Information)

Rx Only

INDICATIONS AND USAGE

Partial-Onset Seizures

VIMPAT (lacosamide) tablets are indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older.

VIMPAT (lacosamide) injection for intravenous use is indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older when oral administration is temporarily not feasible.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including VIMPAT, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI: 1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number of events is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed.

Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1 Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar.

Anyone considering prescribing VIMPAT or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which antiepileptics are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Dizziness and Ataxia

Patients should be advised that VIMPAT may cause dizziness and ataxia. Accordingly, they should be advised not to drive a car or to operate other complex machinery until they are familiar with the effects of VIMPAT on their ability to perform such activities.

In patients with partial-onset seizures taking 1 to 3 concomitant AEDs, dizziness was experienced by 25% of patients randomized to the recommended doses (200 to 400 mg/day) of VIMPAT (compared with 8% of placebo patients) and was the adverse event most frequently leading to discontinuation (3%). Ataxia was experienced by 6% of patients randomized to the recommended doses (200 to 400 mg/day) of VIMPAT (compared to 2% of placebo patients). The onset of dizziness and ataxia was most commonly observed during titration. There was a substantial increase in these adverse events at doses higher than 400 mg/day. [see *Adverse Reactions/*Table 2 (6.1)]

Cardiac Rhythm and Conduction Abnormalities

PR interval prolongation

Dose-dependent prolongations in PR interval with VIMPAT have been observed in clinical studies in patients and in healthy volunteers [see *Clinical Pharmacology* (12.2) in *Full Prescribing Information*]. In clinical trials in patients with partial-onset epilepsy, asymptomatic first-degree atrioventricular (AV) block was observed as an adverse reaction in 0.4% (4/944) of patients randomized to receive VIMPAT and 0% (0/364) of patients randomized to receive placebo. In clinical trials in patients with diabetic neuropathy, asymptomatic first-degree AV block was observed as an adverse reaction in 0.5% (5/1023) of patients receiving VIMPAT and 0% (0/291) of patients receiving placebo. When VIMPAT is given with other drugs that prolong the PR interval, further PR prolongation is possible.

VIMPAT should be used with caution in patients with known conduction problems (e.g. marked first-degree AV block, second-degree or higher AV block and sick sinus syndrome without pacemaker), or with severe cardiac disease such as myocardial ischemia or heart failure. In such patients, obtaining an ECG before beginning VIMPAT, and after VIMPAT is titrated to steady-state, is recommended.

Atrial fibrillation and Atrial flutter

In the short-term investigational trials of VIMPAT in epilepsy patients, there were no cases of atrial fibrillation or flutter. In patients with diabetic neuropathy, 0.5% of patients treated with VIMPAT experienced an adverse reaction of atrial fibrillation or atrial flutter, compared to 0% of placebo-treated patients. VIMPAT administration may predispose to atrial arrhythmias (atrial fibrillation or flutter), especially in patients with diabetic neuropathy and/or cardiovascular disease. Patients should be made aware of the symptoms of atrial fibrillation and flutter (e.g., palpitations, rapid pulse, shortness of breath) and told to contact their physician should any of these symptoms occur.

Syncope

In the short-term controlled trials of VIMPAT in epilepsy patients with no significant system illnesses, there was no increase in syncope compared to placebo. In the short-term controlled trials of VIMPAT in patients with diabetic neuropathy, 1.2% of patients who were treated with VIMPAT reported an adverse reaction of syncope or loss of consciousness, compared to 0% of placebo-treated patients with diabetic neuropathy. Most of the cases of syncope were observed in patients receiving doses above 400 mg/day. The cause of syncope was not determined in most cases. However, several were associated with either changes in orthostatic blood pressure, atrial flutter/fibrillation (and associated tachycardia), or bradycardia.

Withdrawal of Antiepileptic Drugs (AEDs)

As with all AEDs, VIMPAT should be withdrawn gradually (over a minimum of 1 week) to minimize the potential of increased seizure frequency in patients with seizure disorders.

Multiorgan Hypersensitivity Reactions

One case of symptomatic hepatitis and nephritis was observed among 4011 subjects exposed to VIMPAT during clinical development. The event occurred in a healthy volunteer, 10 days after stopping VIMPAT treatment. The subject was not taking any concomitant medication and potential known viral etiologies for hepatitis were ruled out. The subject fully recovered within a month, without specific treatment. The case is consistent with a delayed multiorgan hypersensitivity reaction. Additional potential cases included 2 with rash and elevated liver enzymes and 1 with myocarditis and hepatitis of uncertain etiology.

Multiorgan hypersensitivity reactions (also known as Drug Reaction with Eosinophilia and Systemic Symptoms, or DRESS) have been reported with other anticonvulsants and typically, although not exclusively, present with fever and rash associated with other organ system involvement, that may or may not include eosinophilia, hepatitis, nephritis, lymphadenopathy, and/or myocarditis. Because this disorder is variable in its expression, other organ system signs and symptoms not noted here may occur. If this reaction is suspected, VIMPAT should be discontinued and alternative treatment started.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

been thought to be a potential therapy for SBMA because experiments in mice that were bred to express the mutant androgen receptor showed that reducing androgen levels could mitigate the toxicity of the mutant phenotype.

To evaluate the efficacy and safety of dutasteride (Avodart), Dr. Kenneth H. Fischbeck, chief of the Neurogenetics Branch of the National Institute of Neurological Diseases and Stroke and his colleagues randomized 50 men with SBMA to either 0.5 mg/day of dutasteride or placebo. That dose of dutasteride is the same as that approved for

treating symptomatic benign prostatic hyperplasia.

The men in each group were an average age of about 53 years, and had an average CAG repeat length of 4 codons (compared with wild-type human repeat length of 36 codons or less), a mean duration of weakness of about 12 years, and an average body mass index of about 28 kg/m².

After 2 years, patients treated with dutasteride had virtually no appreciable increase in weight-scaled quantitative muscle assessment scores from baseline—the primary efficacy measure—

whereas the scores in patients taking placebo declined by 5% from baseline. This difference was not significant, according to the investigators, who reported their results in a poster session at the annual meeting of the American Neurological Association.

On the Short Form-36 quality of life questionnaire (version 2), the physical component summary improved by about 14% from baseline for dutasteride-treated patients, which was significantly different from the 10% drop recorded in placebo-treated patients.

Significantly fewer falls occurred

among patients who were treated with dutasteride than among those who received placebo (9 patients reporting 40 falls vs. 16 subjects reporting 63 falls).

However, patients who took dutasteride fared more poorly than those who took placebo on the mental component summary of the questionnaire, in which patients on placebo had a 10% improvement and patients on dutasteride worsened by about 7%.

Modified barium swallow scores, a measurement for dysphagia severity, worsened by a similar amount in subsets of patients from both arms. ■

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 >20× 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 hypoesthesia

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, hypoesthesia, 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