Channel Mutation Implicated in Neuropathies

BY JEFF EVANS

FROM ANNALS OF NEUROLOGY

Mutations in the voltage-gated sodium channel $Na_v1.7$ appear to be the source of chronic pain in nearly 30% of patients with idiopathic small fiber neuropathy, according to a genetic and electrophysiological study of patients with the mutations.

Other gain-of-function mutations in the SCN9A gene that encodes $Na_v1.7$ have been known to cause inherited erythromelalgia and paroxysmal extreme pain disorder, but this is the first time that such mutations have been reported in patients with biopsy-proven idiopathic small fiber neuropathy (I-SFN), reported Dr. Catharina G. Faber of University Medical Centre Maastricht (Netherlands) and her colleagues (Ann. Neurol. 2011 May 20 [doi:10.1002/ana.22485]).

The researchers advised that SCN9A gene analysis might be considered for patients with small fiber neuropathy in whom other causes are excluded, particularly patients with younger ages of onset.

During 2006-2009, Dr. Faber and her coauthors assessed 248 patients who were 18 years and older with a suspected clinical diagnosis of SFN. A total of 185 patients had an underlying cause of SFN, and 19 were lost to follow-up or refused to participate. Inclusion and exclusion criteria were met by the remaining 44 patients. These patients had no identifiable underlying cause of SFN and had normal strength, tendon reflexes, vibration sense, and nerve conduction studies. They also had at least two neuropathic or autonomic symptoms.

Following skin biopsy and quantitative sensory testing (QST), 28 patients met cri-

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Phenylketonurics

VIMPAT oral solution contains aspartame, a source of phenylalanine. A 200 mg dose of VIMPAT oral solution (equivalent to 20 mL) contains 0.32 mg of phenylalanine.

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.

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.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of VIMPAT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorders: Bradycardia

Skin and subcutaneous tissue disorders: Rash

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.

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teria for I-SFN, which included reduced intraepidermal nerve fiber density and abnormal QST. All 28 patients were white.

Overall, 8 (29%) of the 28 patients with I-SFN had a missense mutation in the SCN9A gene. All patients were heterozygous for the mutation. No mutations were detected in SCN9A in 100 healthy control patients. Patients with SCN9A mutations were younger, albeit not significantly, than were the 20 patients without mutations (32.4 years vs. 42.7 years). No other clinical characteristics differed between the two groups.

All but two of the eight reported that their pain, which varied in intensity and quality from patient to patient, began in their distal extremities. Seven of the patients with mutations described autonomic problems.

Electrophysiological analyses of cultured dorsal root ganglion neurons that were transfected with the mutated sodium channels indicated that the mutations changed the function of the channel such that they conferred a hyperexcitable state to the neurons.

Dr. Faber and her associates wrote that the mutations in $Na_v1.7$ may trigger axonal degeneration because "sodium influx is known to impose an energetic load on neurons and neuronal processes, and increased activity of mutant $Na_v1.7$ channels would be expected to have an especially large effect on small-diameter intracutaneous axons."

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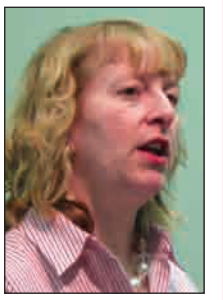
VIEW ON THE NEWS

A Little Less Idiopathic

Small fiber polyneuropathy (SFPN) is one of those common diseases that many have never heard of. Neurologists focus on diseases of myelinated axons, but most axons are unmyelinated and thinly myelinated "small fibers." These tiny axons are invisible to light microscopy and conventional electrophysiology; thus, small fiber diseases remain largely unexplored. In addition, their cardinal symptom is chronic pain, a condition often avoided like a modern plague.



Two recent objective tests, neurodiagnostic skin biopsy and autonomic function testing, now facilitate the diagnosis of small fiber diseases (Neurology 2009;72:177-84) but do not identify their cause. Most SFPN is labeled "idiopathic," which translates from Latin as "we are idiots" and translates for our patients as "no possibility of cure." This study reports that a substantial minority of Dutch SFPN patients have gain-of-function mutations in a sodium channel enriched in small fibers. It will be important to replicate these findings because they come from a carefully selected subset of patients.

These findings remind us that a substantial portion of unexplained chronic pain is neurological, and that neurologists need to engage with such patients. If such mutations are common, testing may develop, along with family-planning questions. The patients will increasingly seek testing and treatment for SFPN, but few neurology groups are currently equipped to do this. Fortunately, any physician can perform skin biopsy and mail the punches to academic or commercial laboratories for analysis. Sodium channel blockers will be used more for treating SFPN and other neuropathic pain. Neurologists will need to learn to prescribe mexiletine and continuous subcutaneous lidocaine along with carbamazepine (Neurology 2004;62:218-25).

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