

Lesions May Resurge After Halting Natalizumab

VITALS

Major Finding: Abrupt discontinuation of natalizumab coincided with a surge in gadolinium-enhancing lesions on MRI that mostly resolved by 9 months without any clinical deterioration.

Data Source: Case series of 11 patients who had received natalizumab infusions before abruptly discontinuing the therapy

Disclosures: Dr. Khan said the study was independently funded and he did not have any financial declarations to make.

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BANGKOK, THAILAND — Patients with multiple sclerosis who abruptly discontinue natalizumab treatment may develop a sudden surge in the number of gadolinium-enhancing lesions apparent on imaging, which seems to resolve by 9 months.

The phenomenon is probably a reaction to the sudden resurging of lymphocytes into the brain—a central nervous system form of immune reconstitution inflammatory syndrome, Dr. Omar Khan said at the World Congress of Neurology.

Although the dramatic imaging changes aren't accompanied by clinical deterioration, about

22% of the lesions did develop into nonenhancing T1 hypointensities, said Dr. Khan, director of the Wayne State University Multiple Sclerosis Clinical Research Center and Radiology Image Analysis Laboratory, Detroit. "Some patients may accumulate a lot of irreversible neuronal damage in this short period of time. And although it's too soon to know for sure, my gut feeling is that over 3 or 4 years, there might be some consequences."

Dr. Khan presented a case series of 11 patients with MS who had received natalizumab infusions before stopping the treatment abruptly. The reasons for discontinuation included infusion site reactions, the development of neutralizing antibodies, changes in insurance cover-

humans at the maximum recommended human dose (MRHD) of 400 mg/day.

When lacosamide (25, 70, or 200 mg/kg/day) was orally administered to rats throughout gestation, parturition, and lactation, increased perinatal mortality and decreased body weights were observed in the offspring at the highest dose. The no-effect dose for pre- and post-natal developmental toxicity in rats (70 mg/kg/day) was associated with a maternal plasma lacosamide AUC approximately equal to that in humans at the MRHD.

Oral administration of lacosamide (30, 90, or 180 mg/kg/day) to rats during the neonatal and juvenile periods of postnatal development resulted in decreased brain weights and long-term neurobehavioral changes (altered open field performance, deficits in learning and memory). The early postnatal period in rats is generally thought to correspond to late pregnancy in humans in terms of brain development. The no-effect dose for developmental neurotoxicity in rats was associated with a plasma lacosamide AUC approximately 0.5 times that in humans at the MRHD.

Pregnancy Registry

UCB, Inc. has established the UCB AED Pregnancy Registry to advance scientific knowledge about safety and outcomes in pregnant women being treated with VIMPAT. To ensure broad program access and reach, either a healthcare provider or the patient can initiate enrollment in the UCB AED Pregnancy Registry by calling 1-888-537-7734 (toll free).

Physicians are also advised to recommend that pregnant patients taking VIMPAT enroll in the North American Antiepileptic Drug Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>.

Labor and Delivery

The effects of VIMPAT on labor and delivery in pregnant women are unknown. In a pre- and post-natal study in rats, there was a tendency for prolonged gestation in all lacosamide treated groups at plasma exposures (AUC) at or below the plasma AUC in humans at the maximum recommended human dose of 400 mg/day.

Nursing Mothers

Studies in lactating rats have shown that lacosamide and/or its metabolites are excreted in milk. It is not known whether VIMPAT is excreted in human milk. Because many drugs are excreted into human milk, a decision should be made whether to discontinue nursing or to discontinue VIMPAT, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of VIMPAT in pediatric patients <17 years have not been established.

Lacosamide has been shown *in vitro* to interfere with the activity of CRMP-2, a protein involved in neuronal differentiation and control of axonal outgrowth. Potential adverse effects on CNS development can not be ruled out. Administration of lacosamide to rats during the neonatal and juvenile periods of postnatal development resulted in decreased brain weights and long-term neurobehavioral changes (altered open field performance, deficits in learning and memory). The no-effect dose for developmental neurotoxicity in rats was associated with a plasma lacosamide exposure (AUC) approximately 0.5 times the human plasma AUC at the maximum recommended human dose of 400 mg/day.

Geriatric Use

There were insufficient numbers of elderly patients enrolled in partial-onset seizure trials (n=18) to adequately assess the effectiveness of VIMPAT in this population.

In healthy subjects, the dose and body weight normalized pharmacokinetic parameters AUC and C_{max} were approximately 20% higher in elderly subjects compared to young subjects. The slightly higher lacosamide plasma concentrations in elderly subjects are possibly caused by differences in total body water (lean body weight) and age-associated decreased renal clearance. No VIMPAT dose adjustment based on age is considered necessary. Caution should be exercised for dose titration in elderly patients.

Patients with Renal Impairment

A maximum dose of 300 mg/day is recommended for patients with severe renal impairment (CL_{CR}≤30mL/min) and in patients with endstage renal disease. VIMPAT is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, AUC of VIMPAT is reduced by approximately 50%.

Therefore dosage supplementation of up to 50% following hemodialysis should be considered. In all renal impaired patients, the dose titration should be performed with caution. [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)* in Full Prescribing Information]

Patients with Hepatic Impairment

Patients with mild to moderate hepatic impairment should be observed closely during dose titration. A maximum dose of 300 mg/day is recommended for patients with mild to moderate hepatic impairment. The pharmacokinetics of lacosamide has not been evaluated in severe hepatic impairment. VIMPAT use is not recommended in patients with severe hepatic impairment. [see *Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)* in Full Prescribing Information] Patients with co-existing hepatic and renal impairment should be monitored closely during dose titration.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

VIMPAT is a Schedule V controlled substance.

Abuse

In a human abuse potential study, single doses of 200 mg and 800 mg lacosamide produced euphoria-type subjective responses that differentiated statistically from placebo; at 800 mg, these euphoria-type responses were statistically indistinguishable from those produced by alprazolam, a Schedule IV drug. The duration of the euphoria-type responses following lacosamide was less than that following alprazolam. A high rate of euphoria was also reported as an adverse event in the human abuse potential study following single doses of 800 mg lacosamide (15% [5/34]) compared to placebo (0%) and in two pharmacokinetic studies following single and multiple doses of 300-800 mg lacosamide (ranging from 6% [2/33] to 25% [3/12]) compared to placebo (0%). However, the rate of euphoria reported as an adverse event in the VIMPAT development program at therapeutic doses was less than 1%.

Dependence

Abrupt termination of lacosamide in clinical trials with diabetic neuropathic pain patients produced no signs or symptoms that are associated with a withdrawal syndrome indicative of physical dependence. However, psychological dependence cannot be excluded due to the ability of lacosamide to produce euphoria-type adverse events in humans.

OVERDOSAGE

Signs, Symptoms, and Laboratory Findings of Acute Overdose in Humans

There is limited clinical experience with VIMPAT overdose in humans. The highest reported accidental overdose of VIMPAT during clinical development was 1200 mg/day which was non-fatal. The types of adverse events experienced by patients exposed to supratherapeutic doses during the trials were not clinically different from those of patients administered recommended doses of VIMPAT.

There has been a single case of intentional overdose by a patient who self-administered 12 grams VIMPAT along with large doses of zonisamide, topiramate, and gabapentin. The patient presented in a coma and was hospitalized. An EEG revealed epileptic waveforms. The patient recovered 2 days later.

Treatment or Management of Overdose

There is no specific antidote for overdose with VIMPAT. Standard decontamination procedures should be followed. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of patient. A Certified Poison Control Center should be contacted for up to date information on the management of overdose with VIMPAT.

Standard hemodialysis procedures result in significant clearance of VIMPAT (reduction of systemic exposure by 50% in 4 hours). Hemodialysis has not been performed in the few known cases of overdose, but may be indicated based on the patient's clinical state or in patients with significant renal impairment.

PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide and Patient Counseling Information section in the Full Prescribing Information.



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DR. KHAN

age, and worries about developing progressive multifocal leukoencephalopathy.

The patients' mean age was 36 years. They had undergone a mean of 13 natalizumab infusions, although that number ranged from 8 to 21. Before taking natalizumab, their mean relapse rate was 1.6/year; the mean relapse rate at discontinuation of the drug was 0.1/year. All patients were negative for John Cunningham (JC) virus.

Before beginning natalizumab, the patients had a mean of 12 T2 lesions, two T1 lesions and 20 gadolinium-enhancing lesions on MRI. Three months after stopping the drug, the numbers of lesions increased significantly, to 17 T2 lesions, 13 T1 lesions, and 137 gadolinium-enhancing lesions. Overall, 93 of the lesions appeared in brain areas that were previously normal-appearing on imaging.

Before natalizumab discontinuation, the mean magnetization transfer ratio value of the gadolinium-enhancing lesions was 31%; at month 3, the mean value had dropped to 19%. "This is a pretty impressive decline, something telling us there might be some fairly intense inflammatory injury on these sites," Dr. Khan said.

Despite the "alarming" scans, Dr. Khan said, the patients did not show corresponding clinical deterioration. Their mean Expanded Disability Status Scale (EDSS) was 3.2 at discontinuation and did not increase significantly by 3 months.

By 9 months, however, the scans had almost universally improved. The mean number of T2, T1, and gadolinium-enhancing lesions had dropped and were not significantly different from the number of lesions seen at baseline.

Clinically, the patients remained stable, Dr. Khan said. Their mean EDSS at 9 months was 4.0—not significantly worse than it was at natalizumab discontinuation. The mean relapse rate was also not significantly different. ■

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