

# NAA Discerns MS From Neuromyelitis Optica

BY MICHELE G. SULLIVAN

BANGKOK, THAILAND — Serum levels of *N*-acetyl aspartate are significantly higher among patients with relapsing-remitting multiple sclerosis and clinical syndromes suggestive of MS than they are in patients with neuromyelitis optica, and might be a valid biomarker to help distinguish the disorders.

In her study of 176 subjects, Dr. Car-

la Tortorella found that serum *N*-acetyl aspartate (NAA) levels were about 14 times higher in those with MS or a clinically isolated syndrome suggestive of MS (CIS) than they were in those with neuromyelitis optica (NMO). In fact, said Dr. Tortorella of the University of Bari, Italy, levels in NMO patients were the same as they were in age-matched healthy controls.

NAA is normally synthesized in neur-

al mitochondria and leaves the cell by several methods, Dr. Tortorella said at the World Congress of Neurology: passing from neurons to oligodendrocytes where it is catabolized; passing through the astrocytes into the extracellular space and thus into the bloodstream; and passing into the cerebrospinal fluid. This process is abnormal in patients with MS, leading to increased serum NAA levels, but no studies have com-

pared these levels in patients with MS and those with NMO.

Dr. Tortorella examined serum and CSF levels of NAA in 48 patients with relapsing-remitting MS, 20 with CIS, and 32 with NMO. She also included 76 age-matched healthy controls for comparison.

There were some baseline differences between the groups. Those with NMO were older (median 43 years) than those with CIS (28 years) or MS (38 years). Disease duration was also different: CIS, 6 months; MS, 6 years; NMO, 5 years.

The Expanded Disability Status Scale score was 1.5 in the CIS group, 2 in the MS group, and 4.6 in the NMO group. None of the MS or CIS patients were tak-

***N*-acetyl aspartate might be a useful way not only to help distinguish between the disorders but also to measure the progression of MS, particularly in its early phase.**

ing disease-modifying drugs, while 10 of the NMO patients were taking immunosuppressants.

All patients submitted serum NAA samples. The levels were similarly high in those with CIS and MS (1.7 mM/L in each group). These were significantly higher than the levels found in those with NMO and among healthy controls (0.12 mM/L each).

While all of the MS and CIS patients had CSF levels available for testing, only eight of the NMO patients did, and there were no CSF samples from healthy controls. "Nevertheless, the CSF NAA levels were markedly and consistently higher in the CIS and MS patients [0.68 and 0.76 mM/L] than they were in the NMO patients [0.05 mM/L]," Dr. Tortorella said.

She found no significant association between NAA levels and age, disease duration, or disease activity. However, among those with MS, she found a significant correlation between increasing NAA levels and worsening Expanded Disability Status Scale scores.

Because the correlation between serum NAA and MS is so much stronger than it is with NMO, Dr. Tortorella suggested that NAA might be a useful way not only to help distinguish between the disorders but to measure the progression of MS, particularly in the early phase of the disease.

The findings make sense in light of the pathology of the various disorders, she said. "One theory is that NAA is higher in MS and CIS because there is more extensive and less focal impairment than there is in NMO, suggesting axonal damage that extends beyond the enhancing lesion. There also could be a defective NAA metabolism in the oligodendrocytes, which are really damaged in MS."

Dr. Tortorella did not have any conflicts of interest to declare. ■

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<sub>max</sub> 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<sub>CR</sub> ≤ 30 mL/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.

VIMPAT tablets and VIMPAT injection



Manufactured for  
UCB, Inc.  
Smyrna, GA 30080

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