Tramiprosate Falls Short in Phase III Alzheimer's Trial

Unusually large placebo effect could be a recurring problem in studies that allow concomitant medications.

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

Tramiprosate, the first antiamyloid drug to enter a phase III trial, was not significantly better than placebo in improving cognitive function in patients with Alzheimer's disease, according to officials of Neurochem Inc., manufacturer of the investigational agent and sponsor of the North American trial.

The negative results are a blow to Alzheimer's disease (AD) researchers and patient advocacy groups, said Dr. Richard J. Caselli, chair of neurology at the Mayo Clinic, Scottsdale, Ariz. "Tramiprosate was the first antiamyloid drug to reach this point, and as such, was widely watched by the Alzheimer's disease community," Dr. Caselli said in an interview. "Its failure to achieve its therapeutic outcomes is therefore very disappointing."

The question now is whether this failure poses a serious challenge to the amyloid hypothesis of AD pathogenesis, he said. "Possibly not, as findings from a newly released study suggest that in addition to its antiamyloid effects, tramiprosate may have a competing effect favoring tau aggregation. It remains too early to heavily discount the amyloid hypothesis, and other trials in progress will be watched expectantly."

The North American Phase III study included 1,052 patients with mild to moderate AD, recruited from 67 sites in Canada and the United States. Patients were randomized to placebo or 100 mg or 150 mg twice daily of tramiprosate. They continued all their concomitant AD drugs during the 18-month study period.

Although there were numerical differences in favor of tramiprosate, those differences failed to reach statistical significance in any of the three primary end points: the Alzheimer's Disease Assessment Scale (ADAS-Cog), the Dementia Rating–Sum of Boxes rating scale (CDR-SB), or magnetic resonance imaging. The MRI analysis showed a trend toward larger hippocampal volume in the active group, although the investigators have not assessed that finding's possible relationship to cognitive performance, Dr. Francesco Bellini, Neurochem's president and chief executive officer, said during the teleconference during which the data were released.

Dr. Bellini hesitated to describe the study as negative, pointing out that the statistical analysis was complicated by improvement in more than 30% of the control patients. "This complicated the analysis beyond expectation, so that our results are inconclusive," Dr. Bellini said.

Dr. Paul S. Aisen, principal investigator of the North American trial, noted the unexpected improvement of so many control patients is probably a result of the effect of concomitant medications, and will be a recurring problem in all long-term studies of disease-modifying agents for AD.

"This problem will not be unique to this program," said Dr. Aisen, professor of neurology at Georgetown University Medical Center, Washington. "It will be faced by anyone who tries to conduct these trials. A number of the approved medications have significant effects on the primary outcomes, and during 18-month trials, these effects will be unavoidable."

Dr. Caselli noted drug companies need to factor this into their trial designs in light of the reality that patients will not be giving up their approved medications while taking a study drug. "We should not infer that study limitations imply the study 'was not really negative, even though it appeared to be,' " he said. "Hopefully the European trial [of tramiprosate] will show something different, but after all is said and done, if both fail and we still encounter the 'Can't tell because they're on treatment' argument, then the study design needs to be changed to accommodate this. But the study was negative as performed."

Despite the failure, 'it remains too early to heavily discount the amyloid hypothesis.'

DR. CASELLI

Dr. Marwan Sabbagh, director of clinical research at the Sun Health Research Institute in Sun City, Ariz., noted the real difficulty with the tramiprosate trial design centers on the lack of objective clinical end points.

"That is the peril of using cognitive outcomes of primary measures," he said in an interview. "Many in the industry would like to see other measures used, but there are none validated or universally agreed upon."

Future studies will need to give equal weight to specific biomarker outcomes, he said, including PET scans, MRI volumetry, and cerebrospinal fluid. "This negative study will make a lot of companies consider their development strategies more carefully."

Neurochem's Dr. Denis Garceau said the company delayed the release of its findings, which were to have been presented publicly in June. In the meantime, Neurochem reworked the statistical analysis and sought advice from the Food and Drug Administration, said Dr. Garceau, who is senior vice president of drug development. "While recognizing the challenges of a trial of this magnitude, the FDA advised that neither the proposed adjusted models nor any further adjustments could be used for this trial to support a positive effect of tramiprosate," Dr. Garceau said.

The data may, however, be used to modify the primary analysis plan for the ongoing European phase III trial, which includes 966 patients in 10 countries. Recruitment for that trial is complete, but significant changes are possible, including changes to the study cohort, duration of treatment, and the statistical analysis, Dr. Garceau said. A company-appointed special advisory board will review the North American trial data, suggest any changes to the European trial, and ultimately recommend to Neurochem the fate of tramiprosate. ■

IEED: Uncertainty Reigns In Diagnosis and Treatment

BY KERRI WACHTER
Senior Writer

BALTIMORE — The lack of diagnostic criteria has hamstrung attempts to diagnose involuntary emotional expression disorder, Dr. Sharon Handel said at a meeting on Alzheimer's disease and related disorders sponsored by Johns Hopkins University.

Even when they make the diagnosis with certainty, physicians have little to offer by way of Food and Drug Administration–approved therapy, said Dr. Handel, of the department of psychiatry and behavioral sciences at Johns Hopkins University, Baltimore. Part of the problem with identifying this condition has been the numerous names under which it is known, she noted. Involuntary emotional expression disorder (IEED) is also known as pseudobulbar affect and pathologic laughing or crying.

Involuntary emotional expression disorder has been associated with Alzheimer's disease, MS, amyotrophic lateral sclerosis, and TBI.

It's estimated that more than 1 million people in the United States have IEED. The disorder has been associated with cerebrovascular accident, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, and traumatic brain injury.

The hallmark of IEED is episodes of crying or laughing that are unrelated to or out of proportion with the eliciting stimulus. There is a disconnection between emotional experience and expression.

Emotional outbursts in IEED are involuntary, episodic, and incongruent with baseline mood. The outbursts are intense, but are followed by a return to baseline.

Disorders of affect—which IEED appears to be—involve impairment of the moment-to-moment regulation of emotion. "There's a disconnection of the neural networks in this condition from the experienced emotion to the display of emotion," Dr. Handel said.

The neural networks of emotion involve the frontal lobes, the limbic system, the brainstem, the cerebellum, and white-matter tracts. In particular, the prefrontal cortex integrates complex sensory and limbic information that determines the emotional valence of a stimulus and modulates motor and autonomic responses involved in emotional expression. It's not clear where the neural interruption occurs in IEED.

For now, the current diagnostic criteria include:

- ► Episodes of involuntary crying, laughing, or related displays.
- ► Origin in brain injury or disease.
- ► A change in the patient's emotional behavior from that prior to the disease or injury.
- ► Incongruent or exaggerated mood.
- ► A response that is excessive or unrelated to the stimulus.
- ► Significant distress or impairment.

The differential diagnosis should include epilepsy; facial dystonia or dyskinesias; vocal tics; axis I disorders (such as major depression or bipolar disorder); axis II disorders (such as borderline personality disorder); and substance abuse.

"These patients often have major depression, and while specific treatment is often the same, I think it's important to differentiate the two conditions," Dr. Handel said.

The differential diagnosis should also include affective lability, essential crying, and witzelsucht. With affective lability, the subjective and objective dimensions of affect are not dissociated. Essential crying is a hereditary and lifelong tendency to cry easily. Witzelsucht is an addiction to trivial joking, which can take the form of an inappropriate giddy affect and irritability or aggressiveness.

In terms of clinical course, IEED frequently remits spontaneously within 6 months. Others may have remission with treatment within 3 months. Resolution of IEED can be independent of the resolution of depression. However, in some cases the disorder is chronic and persistent without treatment.

Treatment of IEED is still evolving. At present, there is no FDA-approved treatment for IEED. "What are typically used—at least up to this point—are SSRIs. They tend to work quite quickly," said Dr. Handel, who has no disclosures.

Dextromethorphan, in combination with quinidine, is being studied to treat patients who have IEED. Dextromethorphan is a nonopioid antitussive, but it also has a number of other neuropharmacologic properties. It is a potent $sigma_1$ agonist (inhibiting the release of the excitatory neurotransmitter, glutamate) and is also an *N*-methyl-D-aspartic acid glutamate receptor antagonist.

Dextromethorphan undergoes significant first-pass metabolism by the cytochrome P450 isoenzyme CYP2D6. Quinidine is a potent inhibitor of this isoenzyme, thereby increasing and sustaining dextromethorphan levels. ■