ALS Progress Unchecked With Use of Lithium

VITALS

Major Finding: ALS patients experienced similar numbers of events (a decline of six or more points on the ALSFRS-R or death) during treatment with lithium plus riluzole or placebo plus riluzole (22 of 40 patients vs. 20 of 44 patients, respectively).

Data Source: Double-blind, randomized, placebo-controlled trial of 84 patients.

Disclosures: The trial was funded by the National Institute for Neurological Disorders and Stroke and the ALS Society of Canada. Mr. Swash and the investigators reported no relevant conflicts of interest.

BY DIANA MAHONEY

The addition of lithium to riluzole for the treatment of amyotrophic lateral sclerosis does not substantially slow disease progression compared with riluzole alone, according to data from a double-blind, randomized, phase II study.

The findings contradict those of a small pilot study that was published in 2008 suggesting that the addition of lithium to standard riluzole therapy led to a slower decline in disease-related disability compared with riluzole therapy alone, according to the lead investigator Dr. Swati P. Aggarwal of Massachusetts General Hospital, Boston, and her colleagues.

The investigators stopped the trial on the recommendation of the data and safety monitoring board and the National Institute of Neurological Disorders and Stroke after the first planned interim analysis showed that lithium in combination with riluzole provided no added benefit over placebo plus riluzole (Lancet Neurol. 2010 April 6 [doi:10.1016/S1474-4422(10)70068-5]).

Although the findings of the phase II study provide "no convincing evidence for the use of lithium as a treatment for patients with ALS," Dr. Aggarwal and her associates wrote that future studies should assess the possibility of smaller beneficial effects of lithium in ALS and the therapeutic potential of compounds that target the induction of autophagy.

The phase II trial of 84 patients with ALS from the United States and Canada used a time-to-event design to try to validate the promising results of the earlier study (Proc. Natl. Acad. Sci. U.S.A. 2008;105:2052-7).

This design allowed the investigators to compare the distributions of how long it took patients to show a decrease of at least six points on the ALS functional rating scale–revised (ALSFRS-R) or to die. The study was designed to have greater than 80% power to detect a 40% decrease in the rate of ALSFRS-R decline if all of the originally planned 250 patients had completed the study, they noted.

In an accompanying editorial, Michael Swash from Barts and the London School of Medicine and Dentistry, London, praised the novelty of the study's time-to-event design, which was powered specifically to detect a major effect of lithium, because of the potential for a rapid result and the possibility of crossover from placebo to treatment (Lancet Neurol. 2010 April 6 [doi:10.1016/S1474-4422(10)70085-5]).

The researchers stopped the trial after the first planned interim analysis showed that lithium in combination with riluzole provided no added benefit over placebo plus riluzole.

"Use of this study design in trials of ALS represents an important advance," he wrote.

"Now all that is required is a drug that has plausible pharmacology and pharmacokinetics, and has a favorable side effect profile, which has been studied in rigorous experiments using SOD1 mice." This tall order, he noted, is "worth striving for."

Of the 40 patients in the lithium group, 1 patient died and 21 had a decrease of at least six points on the ALSFRS-R. In the placebo group, 3 of 44 patients died and 17 had a decrease of six points or more on the ALSFRS-R. In addition to the reported deaths, 18 patients experienced 29 serious events after randomization, with no difference in the rate of occurrence between the two groups, Dr. Aggarwal and her coauthors reported.

The lithium doses in the study ranged from 150 mg to 1,050 mg per day to achieve a serum concentration of 0.4-0.8 mEq/L, which matches the range used in the pilot study, the authors wrote.

Although the investigators could not rule out the possibility of a small positive effect associated with lithium or that other serum concentration ranges could be beneficial, "the lower limit of the 95% CI around the difference in rates of decline of the ALSFRS-R total score was –0.43, suggesting that although a modest benefit of lithium was not ruled out by this study, an effect of 43% or more could be eliminated," they wrote. ■

Pseudobulbar Affect Drug Combo Has No Safety Concerns

BY AMY ROTHMAN SCHONFELD

TORONTO — The combination of dextromethorphan and quinidine to treat pseudobulbar affect does not appear to cause serious cardiovascular adverse events or clinically meaningful changes in QT interval, according to a 12-week, randomized, placebo-controlled trial.

The analysis was undertaken to address safety concerns expressed in October 2006 by the Food and Drug Administration in an approvable letter that the agency sent to Avanir Pharmaceuticals Inc., the company seeking to bring the combination medication (Zenvia) to market.

At a press conference at the annual meeting of the American Academy of Neurology, Dr. Erik P. Pioro, director of the section of ALS and Related Disorders at the Cleveland Clinic, explained that one of the FDA's concerns was the potential for quinidine to have a proarrhythmic effect, even though the dose used for pseudobulbar affect (PBA) is lower than that recommended to treat dysrhythmias. This might be particularly problematic for patients taking higher quinidine doses or those having pre-existing conditions such as torsades de pointes.

"We found no red flags at all that were clinically significant [and] no indication of cardiovascular problems," Dr. Pioro said.

PBA refers to a syndrome of disinhibition of emotional expression. Patients with neurologic conditions such as multiple sclerosis, amyotrophic lateral sclerosis, and Parkinson's disease sometimes display uncontrollable episodes of laughing, crying, or other emotions that have no apparent cause. Patients who have PBA can have more than 30 or more episodes per week.

No drugs are currently approved for the treatment of PBA in the United States. Dr. Pioro said antidepressants are commonly used off-label, with variable efficacy and a high side-effect profile.

Previous work has shown that dextromethorphan, an *N*-methyl-D-aspartate-receptor antagonist and sigma-1-receptor agonist, in combination with quinidine, can reduce the frequency and severity of PBA episodes (Neurology 2004;63:1364-70; Ann. Neurol. 2006;59:780-7). Quinidine is used to increase the bioavailability of dextromethorphan.

VITALS

Major Finding: No serious cardiovascular adverse events or clinically meaningful changes in QT interval were recorded.

Data Source: The STAR trial, a 12-week randomized, placebo-controlled trial of 326 patients with pseudobulbar affect, followed by a 12-week open-label extension phase.

Disclosures: The study was supported by Avanir Pharmaceuticals. Dr. Pioro has received personal compensation for serving as a consultant and scientific advisory board member for Avanir. Dr. Kaye is the chief medical officer of Avanir.

In the STAR trial, the investigators randomized 326 patients to receive 30 mg of dextromethorphan plus 10 mg of quinidine (DMq-30), 20 mg of dextromethorphan plus 10 mg of quinidine (DMq-20), or placebo for 12 weeks. During the first week of the study, patients ingested a single capsule of study drug in the morning, but this increased to twice-daily dosing during weeks 2 through 12. Twelve-lead electrocardiograms were performed at baseline and on days 15, 29, 57, and 84.

Almost 87% of patients completed the trial. Approximately 60% of the patients had ALS, and 40% had multiple sclerosis. Effectiveness was assessed using the Center for Neurologic Study Lability Scale; a minimum score of 13 was needed to enroll in the trial.

Changes in QT interval were considered small and not clinically meaningful, with a mean change of 6.6 msec and 8.3 msec for the DMq-20 and DMq-30 groups, respectively.

Corrected mean changes in QT interval showed changes of less than 5 msec from baseline. No subjects had QT or corrected QT intervals of more than 500 msec at day 84, according to Dr. Randall Kaye, who presented the results at the meeting.

There were few cardiac or vascular adverse events, and none were considered serious. "QT prolonged" was reported in 2 subjects, including one in the placebo group. Neither event was assessed as serious or clinically meaningful.

Eight reports of cardiac adverse events were noted in the treated groups, including sinus bradycardia (two), palpitations (one), AV block first degree (two), tachycardia (one), sinus tachycardia (one), and atrial fibrillation (one).

Dr. Pioro also reported safety and tolerability results of a 12-week open-label extension of the STAR trial that enrolled 253 of the 283 patients who completed the double-blind trial; all of these patients received the DMq-30 combination.

During this open-label extension, no treatment-related or cardiovascular serious adverse events were reported. A total of 74% of patients reported one or more adverse events, with similar rates reported no matter which group they had been in during the controlled trial. ■