Brain Trauma Trials May Finally Be Paying Off

BY BETSY BATES
Los Angeles Bureau

HONOLULU — Disappointing clinical trial results should not suggest that outcomes cannot be improved in traumatic brain injury, only that methodologies may need to be refined and study populations equalized as promising approaches come to the fore, Dr. D. James Cooper said during a plenary address at the annual congress of the Society of Critical Care Medicine.

To be sure, meaningful advances have been elusive, with various interventions producing hopeful improvements in animal models, then fizzling in human trials.

But the heterogeneity of the traumatic brain injury (TBI) population and "huge differences" in the specific trauma suffered may make study results look unfairly pessimistic, said Dr. Cooper, deputy director of the intensive care unit at Alfred Hospital, Melbourne.

Experimental treatments may be initiated too late, often because of logistical and informed-consent dilemmas, and older patients may be so unlikely to benefit that they negatively skew results.

Follow-up assessment periods may be too brief, because it increasingly appears that Glasgow Outcome Scale scores improve greatly over time, but at a very slow pace, he said.

A number of lessons have indeed been learned, even from negative clinical trials, and several promising approaches are currently under review.

Serious doubt has been cast on the efficacy of early high-dose steroids, for example, following the curtailment of the 10,000-patient randomized controlled MRC-CRASH (Corticosteroid Randomisation After Significant Head Injury) trial in the United Kingdom after excess deaths were reported in the steroid arm.

"It seems clear from the study that the use of an agent that has been very widely used, particularly in the developing world, clearly and unambiguously increases mortality, accounting for an absolute number of 3% excess deaths. I think it's abundantly clear … [that the] use of high-dose steroids should cease," said Dr. Cooper, who also serves as associate director for Australia's National Trauma Research Institute.

Because they lower vasopressor requirements in TBI patients, lower-dose steroids are used quite commonly in the intensive care environment, he noted.

"There are no randomized controlled trials at all in this area, and it's clear to me, [based on the unequivocal MRC-CRASH results, that] there needs to be … a reevaluation" of this practice, said Dr. Cooper.

Another unexpected finding stemmed from the Australian SAFE-TBI (Saline Versus Albumin Fluid Evaluation–Traumatic Brain Injury) study, in which Dr. Cooper participated. That study of nearly 500 patients confirmed that albumin is independently associated with mortality in TBI patients when it is used for intravascular fluid resuscitation in the first 28 days. In contrast, saline was associated with lower mortality and better neurologic outcomes in patients with moderate to severe TBI.

The reasons remain unclear, although Dr. Cooper hypothesized that albumin may increase brain edema, prompting the use of other agents that could contribute to mortality; that it may increase bleeding or cause more coagulopathy; or that it may be the result of hemodilution.

A recent analysis of data from both the SAFE-TBI study and the earlier ATBIS (Australasian Traumatic Brain Injury Study) "[adds] to our strong feeling that saline alone might be worthwhile," he said.

As a final note, Dr. Cooper outlined two ongoing international clinical trials of early decompressive craniectomy to reduce intracranial pressure, an approach he said may offer "considerable promise."

The notion of temporarily removing the anterior portion of the skull is not a new idea, he stressed. But it has been controversial and not well studied, despite striking findings of benefit among young patients in small trials.

For example, the absolute risk of mortality was halved with early decompressive craniectomy versus medical therapy alone in a recent, 38-patient French study; but the trial was concluded early because of slow recruitment.

Dr. Cooper's government-sponsored DECRA (Early Decompression Craniectomy in Patients With Severe Traumatic Brain Injury) trial at 21 international sites (including 2 in the United States) is enrolling only patients younger than 60 years old with blunt diffuse brain injuries—strict criteria that may be more conducive to interpreting results, he said.

Thus far, 112 patients have been enrolled of 165 anticipated, which is "already many, many times higher than the largest study ever conducted of early decompressive craniectomy," Dr. Cooper noted.

Among the first 42 patients randomized to receive surgery, the complication rate has been less than 10%, he said. ■

No Cognitive Benefit Seen for Donepezil

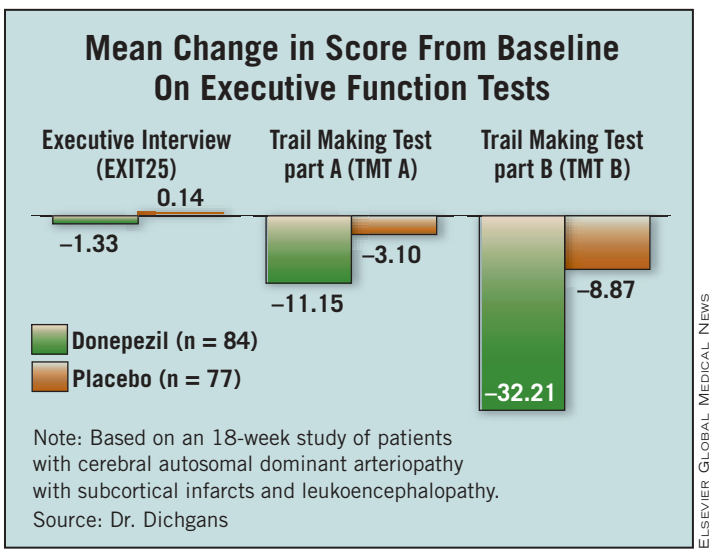
BY SHARON WORCESTER
Southeast Bureau

NEW ORLEANS — Donepezil had no effect on cognitive impairment in a recent study of patients with vascular dementia, but the acetylcholinesterase inhibitor was associated with significant improvement on several measures of executive function, Dr. Martin Dichgans reported at International Stroke Conference 2008.

Cholinergic deficits might contribute to cognitive impairment in vascular dementia, and donepezil has been shown to improve measures of functioning, but because most trials of the drug include patients with Alzheimer's disease, it is difficult to determine whether the effects of the drug result from improvements in cognition or improvement in the Alzheimer's disease.

For the current study, 168 patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) were included in the randomized double-blind study, which was a phase II proof of concept study. CADASIL is an early-onset form of subcortical ischemic vascular dementia that is unlikely to overlap with Alzheimer's disease, making it a condition well suited for testing the effects of donepezil on cognitive functioning, said Dr. Dichgans of Ludwig-Maximilians University, Munich.

Patients received 5 mg of donepezil or placebo daily for the first 6 weeks of the 18-week trial, then 10 mg daily thereafter; the primary end point was a change from baseline in Vascular-Alzheimer's Disease Assessment Scale-Cognitive subscale (V-ADAS-cog) score, said Dr. Dichgans, who serves as a consultant for Eisai Co., which makes donepezil and sponsored the study.



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There was no statistically significant difference between the treatment and placebo groups in regard to the change from baseline V-ADAS-cog scores, but a significant difference was noted between the groups on Trail Making Test part A (TMT A) time and Trail Making Test part B (TMT B) time, which assess the time required to perform specific tasks, and on the Executive Interview (EXIT25), which assesses executive cognitive function. (See box.)

A trend toward improvement on the clock drawing tests CLOX 1 and CLOX 2 scores—which measure executive cognitive function deficits and posterior cortical impairment, respectively—was also seen in the treatment group, compared with the placebo group, Dr. Dichgans said at the conference, which was sponsored by the American Stroke Association.

For the treatment group, CLOX1 score improved from baseline by 0.76, compared with 0.09 for placebo. For the CLOX2 group, treated patients' score improved by 0.52 from baseline, versus 0.05 for patients on placebo.

Clinical relevance of findings on processing speed is unknown, he noted.

Patients in the study had a mean age of 55 years. Inclusion criteria included a baseline score of 10-27 on the Mini-Mental State Exam or a TMT B score that was 1.5 standard deviations below the mean after adjusting for age and education. ■