

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 in-

creases 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. ■

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(3% and <1%); Anorgasmia* (2% and <1%); *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo > Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflamed injury, anxiety. *Primarily ejaculatory delay. †Denominator used was for males only (N=225 Lexapro; N=188 placebo). ‡Denominator used was for females only (N=490 Lexapro; N=404 placebo). Generalized Anxiety Disorder Table 3 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see TABLE 3). TABLE 3. Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder (Lexapro (N=429) and Placebo (N=427)).

Autonomic Nervous System Disorders: Dry Mouth (9% and 5%); Sweating Increased (4% and 1%); Central & Peripheral Nervous System Disorders: Headache (24% and 17%); Paresthesia (2% and 1%); Gastrointestinal Disorders: Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Ralutance (2% and 1%); Toothache (2% and 0%). General: Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%); Musculoskeletal: Neck/Shoulder Pain (3% and 1%). Psychiatric Disorders: Somnolence (13% and 7%); Decreased (3% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%). Urogenital: Ejaculation Disorder^{1,2} (14% and 2%); Anorgasmia¹ (6% and <1%); Menstrual Disorder (2% and 1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo > Lexapro: inflamed injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=182 Lexapro; N=195 placebo). †Denominator used was for females only (N=247 Lexapro; N=232 placebo). Dose Dependency of Adverse Events The potential dose dependency of common adverse events (defined as an incidence rate of ≥5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). Table 4 shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. TABLE 4. Incidence of Common Adverse Events* in Patients with Major Depressive Disorder Receiving Placebo (N=111), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=125): Insomnia (4%, 7%, 14%); Diarrhea (5%, 6%, 14%); Dry Mouth (3%, 4%, 9%); Somnolence (1%, 4%, 9%); Dizziness (2%, 4%, 7%); Sweating Increased (<1%, 3%, 8%); Constipation (1%, 3%, 6%); Fatigue (2%, 2%, 6%); Indigestion (1%, 2%, 6%); Adverse events with an incidence rate of at least 5% in either the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. Male and Female Sexual Dysfunction with SSRIs Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Table 5 shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. TABLE 5. Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials (In Males Only: Lexapro (N=407) and Placebo (N=383)); Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%). (In Females Only: Lexapro (N=737) and Placebo (N=596)); Libido Decreased (3% and 1%); Anorgasmia (3% and <1%) There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. Vital Sign Changes Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. Weight Changes Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. Laboratory Changes Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. ECG Changes Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. Other Events Observed During the Premarketing Evaluation of Lexapro Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in Tables 2 & 3, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1,000 patients; Cardiovascular - Frequent: palpitation, hypertension. Infrequent: bradycardia, tachycardia, ECG abnormal, flushing, varicose vein, Central and Peripheral Nervous System Disorders - Frequent: light-headed feeling, migraine. Infrequent: tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. Gastrointestinal Disorders - Frequent: heartburn, abdominal cramp, gastroenteritis. Infrequent: gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. General - Frequent: allergy, pain in limb, fever, hot flashes, chest pain. Infrequent: edema of extremities, chills, lightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. Hemic and Lymphatic Disorders - Infrequent: bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. Metabolic and Nutritional Disorders - Frequent: increased weight. Infrequent: decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. Musculoskeletal System Disorders - Frequent: arthralgia, myalgia. Infrequent: jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. Psychiatric Disorders - Frequent: appetite increased, lethargy, irritability, concentration impaired. Infrequent: jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruising, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. Reproductive Disorders/Female - Frequent: menstrual cramps, menstrual disorder. Infrequent: menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. *% based on female subjects only. N= 905 Respiratory System Disorders - Frequent: bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. Infrequent: asthma, breath shortness, laryngitis, pneumonia, tracheitis. Skin and Appendages Disorders - Frequent: rash. Infrequent: pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry flake, skin nodule. Special Senses - Frequent: vision blurred, tinnitus. Infrequent: taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. Urinary System Disorders - Frequent: urinary frequency, urinary tract infection. Infrequent: urinary urgency, kidney stone, dysuria, blood in urine. Events Reported Subsequent to the Marketing of Escitalopram - Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing evaluation and were not observed during the premarketing evaluation of escitalopram: abnormal gait, acute renal failure, aggression, akathisia, allergic reaction, anger, angioedema, atrial fibrillation, chorea-thetosis, delirium, delusion, diplopia, dysarthria, dyskinesia, dystonia, ecchymosis, erythema multiforme, extrapyramidal disorders, fulminant hepatitis, hepatic failure, hypoaesthesia, hypoglycemia, hypokalemia, INR increased, gastrointestinal hemorrhage, glaucoma, grand mal seizures (or convulsions), hemolytic anemia, hepatic necrosis, hepatitis, hypotension, leucopenia, myocardial infarction, myoclonus, neuroleptic malignant syndrome, nightmare, nystagmus, orthostatic hypotension, pancreatitis, paranoia, photosensitivity reaction, priapism, procloniaemia, prothrombin decreased, pulmonary embolism, QT prolongation, rhabdomyolysis, seizures, serotonin syndrome, SIADH, spontaneous abortion, Stevens Johnson Syndrome, tardive dyskinesia, thrombocytopenia, thrombosis, torsade de pointes, toxic epidermal necrolysis, ventricular arrhythmia, ventricular tachycardia and visual hallucinations.

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No Cognitive Benefit Seen for Donepezil

BY SHARON WORCESTER
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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.

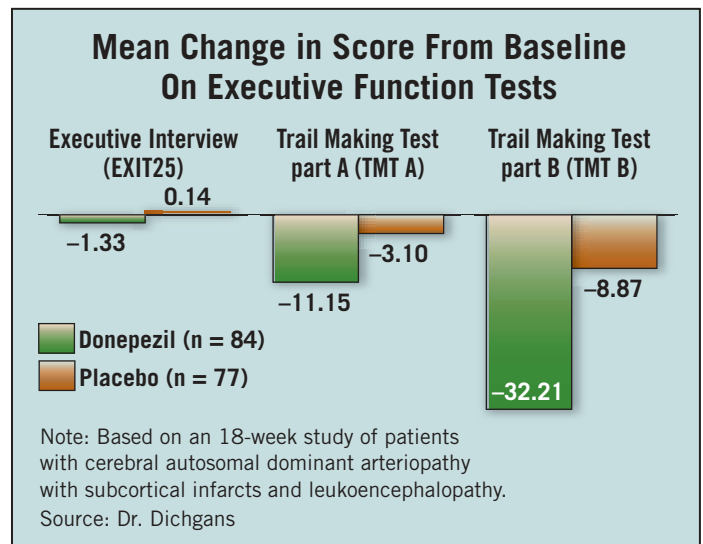
For the current study, 168 patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) were included in the randomized double-blind study, which was a phase II proof of concept study. CADASIL is an early-onset form of subcortical ischemic vascular 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.

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 functioning. (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. ■

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