SSRI of No Help for Depression in Heart Failure

BY DAMIAN McNAMARA

HOLLYWOOD, FLA. — Sertraline did not significantly improve depressive symptoms or cardiovascular status among depressed patients with heart failure, compared with placebo in a 12-week, randomized, double-blind study.

A second, posthoc analysis of the data indicates patients who achieve depression remission experience prognostic and functional improvements, including statistically fewer mean cardiovascular events during long-term follow-up, compared with nonremitters.

Dr. Wei Jiang presented results of both the primary and secondary analyses of the Sertraline Antidepressant Heart Attack Randomized Trial in Congestive Heart Failure (SADHART-CHF) at a meeting of the New Clinical Drug Evaluation Unit (NCDEU) sponsored by the National Institute of Mental Health.

She and her associates assessed depressive symptoms, cardiovascular status, and long-term mortality rates between 234 patients randomized to sertraline (Zoloft, Pfizer Inc.) and an additional 235 who received placebo in an intent-to-treat analysis. At the end of the 12-week trial, there were 144 patients remaining on treatment and 146 others in the placebo group.

There was a significant reduction in Hamilton Depression Rating Scale scores in both groups, compared with baseline. However, no significant differences were found between groups in these Hamilton scores, composite cardiovascular scores, fatal or nonfatal cardiovascular events, or results of the Kansas City Cardiomyopathy Questionnaire. In addition, long-term survival did not differ significantly between groups.

The null findings might result from an effect of a nurse-facilitated supportive intervention for all participants, Dr. Jiang said. "But a placebo effect cannot be ruled out."

Dr. Jiang receives research support from the NIMH (sponsor of the study), the National Heart, Lung, and Blood Institute, and from Pfizer for an unrelated study. Pfizer's only role in SADHART-CHF was to supply the sertraline, she added.

"We spent 6 years doing the study, and now we are stuck ... Other than sertraline, almost all other classes of antidepressants … have cardiovascular concerns," said Dr. Jiang, who is on both the internal medicine and the psychiatry and behavioral sciences faculties at Duke University, Durham, N.C.

The 469 participants in the primary analysis were 45 years or older, had a New York Heart Association classification of II or higher, and a left ventricular ejection fraction of 45% or less. Mean age was 63 years in the treatment cohort and 62 years in the placebo group. Men comprised 57% and 62%, respectively, of these cohorts.

Those randomized to treatment received sertraline between 50 mg/day and 200 mg/day or matched placebo. The average sertraline dose was 69 mg/day and 75 mg/day for placebo. "That is too low," a meeting attendee said during a question-and-answer session. "That is what we thought, also," Dr. Jiang said. "I agree with you, but we felt many patients would drop out [if dosing were higher]. Remember that 41% of the sertraline arm dropped out."

The same person commented further that sertraline might have been more effective at a higher dose. "There are studies showing 50 mg is enough, so I don't know the right answer," she replied.

Dr. Jiang also presented results of a posthoc analysis of remission using Hamilton Depression scores. Remission was associated with prognostic and functional improvement in depressed heart failure patients during the 12-week intervention phase. In addition, there was a statistical difference in mean overall cardiovascular events, that favored remitters (1.11) versus nonremitters (1.66) during follow-up.

Again, there was no significant difference in long-term survival between the 208 remitters and 194 nonremitting patients (mean survival of 866 days versus 793 days). The remaining 67 patients were classified as early terminators because they dropped out of the study prior to the first treatment.

Achievement of remission should be a target for additional studies of patients with heart failure and comorbid depression, Dr. Jiang said. In addition, more data are needed to identify factors that might indicate which heart failure patients are likely to respond to different antidepressant modalities, she said. ■

NIMH Brain Researchers: Some Children Outgrow ADHD

BY JANE SALODOF MacNEIL

SANTA FE, N.M. — Twenty years of brain imaging studies in children are leading National Institute of Mental Health investigators to explore whether they can distinguish youngsters who will outgrow attention-deficit/hyperactivity disorder from those for whom it will be a persistent problem.

This new work is built on evidence that normal brain development occurs with a 3-year delay in children with ADHD. In pilot data, the researchers have found a hint that the brains of youngsters who have "good" clinical outcomes compensate for this delay, whereas those of youngsters with "poor" outcomes take a different developmental trajectory.

"Approximately half of them grow up, and follow what their grandmothers said all along: 'He will grow out of it,' " Dr. Judith L. Rapoport, chief of the Child Psychiatry Branch at the NIMH, told attendees at an annual psychiatric symposium sponsored by the University of Arizona.

Her group has accumulated more than 6,000 anatomic MRIs of children whose brains were scanned every 2 years starting at age 4 in a longitudinal study, she said. The subjects were not selected for any particular psychiatric condition, but 300 were subsequently diagnosed with ADHD. In addition, the investigators received 3,000 referrals of children with suspected childhood-onset schizophrenia, among whom it found and scanned 107 children with the rare disorder.

By mapping the normal course of cortical development, the study revealed a process of cortical thinning from ages 5 to 20 that can be seen in Dr. Rapoport's words as "a back-to-front wave of cortical maturation" (PNAS 2004;101:8174-9; Nat. Neurosci. 1999;2:861-3). Comparison of high-intelligence children with those of high and average intelligence subsequently showed the children with high IQs had a developmental trajectory in which key measures were reached 2-3 years later than in the other children.

"We were simply astonished to find out the real difference was between the superior intelligence group and the rest, and it was in the frontal lobes," Dr. Rapoport recalled, adding that this is "one example that later at least in some brain regions is not associated with deficit and may be associated with the opposite."

Subsequent work showed later cortical development in the brains of children with ADHD (PNAS 2007;104:19649-54), and that the trajectory of baseline thinning also differed in ADHD between children with better outcomes and those with poor outcomes. Among the findings were that brain asymmetry is not as pronounced in ADHD as in normal children and that the right parietal cortex—a little region that "looks like a freckle"—develops differently in ADHD.

One study showed that cortical thickness "normalizes" in the right parietal cortex of 48 children with ADHD who have "good" outcomes. The difference at a key point in the developmental trajectory was statistically significant when these children were compared with 51 children with poor outcomes and to 161 healthy children without ADHD. The finding "suggests compensatory plastic response for good-outcome subjects," Dr. Rapoport said of the ongoing study.

Further work suggests that some children with ADHD reach a developmental milestone by their adolescent years, but others do not. She cautioned that her group has not published what it considers "just pilot data" in this regard, but has started to follow 80 hyperactive 5-year-olds in the hope of developing a predictive test based on brain development trajectories that will distinguish the children who are going to outgrow ADHD from "those who are going to continue to have problems."

The study should produce results in about 5 years, Dr. Rapoport said, forecasting that such a test might help clinicians "single out people for whom resources are really needed, and let us relax more for people for whom, no matter what you do, it is going to turn out fine."

Treating ADHD with stimulants remains controversial, and there is not good evidence supporting benefit from long-term use, she noted. Her group has found no difference in brain development trajectories when children on stimulants are compared with children not treated with stimulants, she said. That said, she suggested, "Kids' memories of grade school are happier [when given stimulants], because they weren't at odds with everyone all the time."

For now, Dr. Rapoport strongly discourages parents from spending money on brain imaging tests to diagnose ADHD. While useful for research, the tests currently available are unlikely to have sufficient sensitivity or specificity "that you would want anyone to pay for," she said. ■

Predicting Schizophrenia in the Womb

Prenatal screening based on variations in the numbers of certain key genes might be able to identify the carriers of childhood-onset schizophrenia and other psychiatric disorders, according to Dr. Rapoport.

About 9% of children with childhood-onset schizophrenia have been found to have genetic abnormalities, Dr. Rapoport explained. When children with multiple copies or deletions of key genes are counted, the proportion with possible genetic markers rises to 36%.

Moreover, many of the genes also are implicated in autism. Both conditions are associated with ahead-of-normal brain development, she said, and the timing of certain milestones might determine which of these or other disorders develops. Of note, three children referred to the team as possibly having childhood-onset schizophrenia subsequently developed bipolar disorder instead.

"I think the world is going to be stood on its head diagnostically when these things get sorted out," Dr. Rapoport said, estimating that as many as 50% of children with early neurodevelopmental abnormalities could have copy number variants.