New Drug Slows Decline In Mild Alzheimer's Cases

BY KERRI WACHTER
Senior Writer

SAN JUAN, P.R. — R-flurbiprofen, one of a new class of selective amyloid-β 42–lowering drugs, shows some promise at higher doses in delaying cognitive and functional declines associated with Alzheimer's disease, according to phase II trial data presented at the annual meeting of the American Association for Geriatric Psychiatry.

"Subjects with mild AD on the high dose (800 mg) showed a reduced rate of decline on all of the primary outcome measures," said Dr. Daniel D. Christensen, a psychiatrist and neurologist at the University of Utah, Salt Lake City. This selective amyloid-β 42–lowering agent (SALA) is thought to be an allosteric modulator of γ-secretase.

Patients who took the higher dose of R-flurbiprofen showed a 34% effect size at 12 months, though this was not statistically significant.

The proof-of-concept study involved 207 patients with mild to moderate Alzheimer's disease (AD), and was conducted in Canada and the United Kingdom. The trial was sponsored by the drug's developer, Myriad Pharmaceuticals Inc. Dr. Christensen also is a consultant/speaker for the company.

Patients were randomized to receive twice-daily doses of 400 mg R-flurbiprofen, 800 mg R-flurbiprofen, or placebo. The placebo-controlled portion of the trial lasted for 12 months. All trial participants who were stable on anticholinesterase drugs for at least 3 months prior to the study were allowed to continue with them. Patients were assessed using the Alzheimer's Disease Assessment Scale, cognitive section (ADAS-cog), the Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL), and the Clinical Dementia Rating (CDR) sum of box score.

"There was essentially no response in the moderate patients," said Dr. Christensen. For this reason, the researchers limited their analysis to patients with mild AD (those with a Mini-Mental State Examination score of at least 20). Of the patients who had mild Alzheimer's, 46 received placebo, 36 received 400 mg R-flurbiprofen, and 48 received 800 mg R-flurbiprofen.

In terms of ADAS-cog scores, those who received 400 mg R-flurbiprofen had essentially the same response as those on placebo. Those taking the higher dose of R-flurbiprofen showed a 34% effect size at 12 months, though this was not statistically significant. "This basically means that we prevented 34%—about a third—of the respective decline" seen in the other two groups, Dr. Christensen said.

Those in the 800-mg group showed an effect size of 45% at 12 months, as measured by the ADCS-ADL, though this did not reach statistical significance. The 400-mg dose appeared to have an intermediate effect on daily function. There was little difference at 12 months between the placebo group and those in the 400-mg group in global function, as measured by the CDR. The effect size for the 800-mg group was 36%, though this did not reach statistical significance.

In an exploratory analysis, the researchers found a significant relationship between plasma concentration and response. A total of 29 patients (60% of those in the 800-mg group) had drug plasma concentrations greater than 75 μg/mL.

Both dosing regimens were generally well tolerated, Dr. Christensen said. The numbers of discontinuations attributable to adverse events were comparable among the placebo group and the two active treatment groups. Transient eosinophilia, mild anemia, blood pressure elevation, lower respiratory tract infections, and mild rashes occurred more frequently in the active treatment groups.

Patients in Canada were allowed to participate in a follow-on study after 12 months. Of the 106 patients eligible, 86 enrolled for an additional 12 months; 62 had mild AD. Of the mild-AD patients, 20 had previously been in the placebo group and were randomized to receive either 400 mg or 800 mg R-flurbiprofen twice daily.

A phase III trial is now underway in the United States. ■

Aripiprazole Found Effective in Prolonged, Comorbid Delirium

BY JANE SALODOF MACNEIL
Southwest Bureau

SANTA ANA PUEBLO, N.M. — Aripiprazole should be considered for treatment of prolonged delirium, especially in patients with significant medical comorbidity, Dr. David Straker said at the annual meeting of the Academy of Psychosomatic Medicine.

Dr. Straker reported that the atypical antipsychotic reduced Delirium Rating Scale-revised-98 scores by 50% or more for 12 of 14 patients in a case series at New York Presbyterian Hospital, Columbia University Medical Center in New York City. The average score fell from 25.1 to 9.4.

All 14 patients improved, according to Dr. Straker, now at Zucker Hillside Hospital, Long Island Jewish Medical Center, Glen Oaks, N.Y. Eight came off restraints, and six no longer required constant observation after treatment with aripiprazole (Abilify). "In this small case series, aripiprazole appeared to be safe and effective. Adverse side effects were minimal," Dr. Straker said. "Aripiprazole may have a role in hypoactive, lethargic patients with delirium."

Dr. Lawson R. Wulsin of the University of Cincinnati called the study much needed and urged that its results be shared with hospital physicians who are not psychiatrists. He said he hoped the "promising findings" would provide the impetus for an open-label or randomized clinical trial.

In an interview at the meeting, Dr. Straker said his schedule since completing a fellowship at Columbia did not allow him to organize a trial, but that one was needed, and he would like to participate. "I think it should be studied further," he said. "Right now there is no drug that is Food and Drug Administration–approved for delirium. There is nothing out there." Dr. Straker said he studied aripiprazole because it had not been tried for delirium and had the potential for fewer side effects than other antipsychotic agents. Hospital patients who develop delirium often have comorbidities, he said, presenting chart reviews of 21 patients with delirium.

In this unpublished series, he found that most had cardiovascular problems before treatment. Two-thirds had impaired glycemic control. Dyslipidemia, hypertension, and metabolic syndrome occurred in more than half. Nine were obese, and eight had QTc intervals greater than 450 milliseconds on their electrocardiograms.

"You might say in acute patients, why worry?" he challenged the audience, answering, "After delirium is resolved, we don't abruptly stop antipsychotics." Many patients stay on antipsychotic medication long after leaving the hospital, according to Dr. Straker. Patients released to nursing homes may be kept on a drug for months before being reevaluated.

The 14 patients in the case series (eight women and six men) were 71 years old on average and had a mean score on the Clinical Global Impression (CGI) severity scale of 5.2. Dyslipidemia, hyperglycemia, hypertension, and metabolic syndrome were reported in more than half before treatment. Cardiovascular disease, cerebrovascular disease, and QTc prolongations were also reported but in a smaller proportion.

Dr. Straker said the etiology of delirium was varied. He cited medications, infection, surgery, dementia, and HIV as underlying factors. The average aripiprazole dose was 8.9 mg per day, with only two patients receiving more than 10 mg per day. Patients reached maximum treatment response in an average of 6.2 days, with a mean improvement of 2.1 on the CGI scale. Four patients had been given haloperidol during the first few days of their delirium.

Two patients died after discontinuing aripiprazole: one of sepsis, the other of respiratory failure after pneumonia. Among the adverse events that did not occur, Dr. Straker listed torsades de pointes, cardiac and cerebrovascular events, diabetic ketoacidosis, significant extrapyramidal effects or akathisia, dysphagia, and falls. He reported that average QTc decreased, with just one patient having it rise beyond 450 milliseconds. Fasting blood glucose fell from 176.1 mg/dL to 116.2 mg/dL, and no patient had a worsening of glycemic control. ■

Primary Docs Often Overlook Depressive Symptoms in Elderly

BY KATE JOHNSON
Montreal Bureau

ORLANDO — Depression in elderly patients is easily missed by primary care physicians, according to a new study.

"Sometimes family doctors don't have time to screen for depression, and patients don't put it out on the table," said Dr. Irene Mangani, who presented her findings in a poster at the annual meeting of the Gerontological Society of America.

"These people can be helped with a lot of interventions for depression, not just pharmacological interventions but also psychotherapy and exercise. And we miss these opportunities by not screening them for depression," said Dr. Mangani, who is a geriatrician at the University of Florence, Italy. Her investigation included data from the ICARe Dicomano Study, which enrolled two waves of community-dwelling individuals, aged 65 years and older. The first group was enrolled in 1995, the second in 1999.

A total of 656 participants (mean age 74 years) completed the 30-item Geriatric Depression Scale (GDS), and their scores were compared with evaluations by primary care physicians who assessed the participants for depressive symptoms.

Using a GDS cutoff of 14 or higher to identify depression, the investigators found that the prevalence of depressive symptoms was 24% in the 1995 wave of participants and 31% in the 1999 wave. However, primary care physicians identified only a 14% prevalence in the first wave and 11% in the second wave.

"The GDS is not a diagnosis of depression. It is a screening tool that identifies depressive symptoms. But if someone has a GDS score higher than 14, they should be asked about other symptoms of depression because if they are depressed, this condition can be cured and can be dangerous if not taken care of," Dr. Mangani said in an interview.

She said depression in this population has been linked with higher disability and mortality rates, making screening worthwhile, even in the primary care setting where there is so little time.

"Just asking a simple question like 'have you lost interest in things you usually like?' is something that doesn't take much time but can be important. If they answer yes, you can ask more questions or even give them the GDS screen," she said. ■