Atorvastatin May Slow Alzheimer’s Progression

BY BRUCE JANCIN
Denver Bureau

NEW ORLEANS — High-dose atorva-
statin in patients with Alzheimer’s disease
delayed progression and improved depressive symptoms in a
two- to four-fold minority randomized,
double-blind trial, D. Larry Sparks, Ph.D., said
to the annual scientific sessions of the
American Heart Association.

The finding adds to the growing number of studies that highdose statin therapy for the cognitive and behavioral manifestations of Alzheimer’s dementia must await completion of two ongoing large multicenter clinical trials, but the results of this single center 1-year pilot study are certainly promising, said Dr. Sparks, senior scientist and head of the Ralph and Muriel Roberts Laboratory for Neurodegenerative Re-
search at the Sun Health Research Insti-
tute, Sun City, Ariz.

He reported on 46 patients with mild to moderate Alzheimer’s disease who completed 1 year on 80 mg/day of atorvastatin or placebo in addition to whatever cholinesterase inhibitors they were already on at randomization.

Primary outcomes in the study were change in the cognitive portion of the Alzheimer’s Disease Assessment Scale (ADAS-cog) and the Alzheimer’s Disease Cooperative Study-Clinical Global Im-
pression of Change (ADCS-CGIC), both administered quarterly.

From a mean baseline score of 20 on the ADAS-cog, both the atorvastatin and placebo groups showed deterioration at 3 months. Thereafter, scores in the statin group stabilized, but the placebo group continued to deteriorate by about 1 point per quarter, so that at 1 year the atorva-
statin group had a mean 3.5-point superi-
or score on this instrument.

Mean ADCS-CGIC scores declined with time in both groups. However, the rate of decline was consistently steeper in the placebo arm, with the between-group differ-
ences missing statistical significance by the last quarter of margins at both 9 and 12 months, Dr. Sparks continued.

Mean scores at 1 year on the Geriatric Depression Scale improved from 6 to 4 in the atorvastatin group while deteriorating to 8 in the placebo arm—a significant be-
tween-group difference.

Scores on the 10-item Neuropsychiatric Inventory declined from a baseline of 7.5 in the atorvastatin group to 6.7 in the placebo group at 1 year. Mean scores on the Mini-Mental State Examination re-
mained stable over time in the atorvastatin group—20.8 at baseline and 20.4 at 1 year—
while declining to 18 in the placebo group. Performance on the ADCS Activities of Daily Living scale at 6 and 12 months did not show any strong between-group differ-
ences. Levels serum of superoxide dismu-
tase and glutathione peroxidase activity were unchanged by high-dose atorvastatin; however, mean circulating ceruloplasmin levels were reduced 10%-15% at various time points, compared with placebo.

Dr. Sparks noted that animal studies suggest cholesterol in the brain plays a key role in production of B-amylloid, the putative neurotoxin believed to precipitate Alzheimer’s disease. While the blocked reductions in circulating total, LDL, and VLDL cholesterol achieved with high-
dose atorvastatin in the study are consist-
ent with a lipid-lowering mechanism for the apparent cognitive and depressive bene-
fits, statins also improve vascular endo-
theial function and have anti-inflammatory effects that might be relevant.

During a press conference, he said that serum cholesterol is the culprit contribut-
ing to Alzheimer’s. By choosing a drug that does not cross the blood-brain barri-
er, he showed that lowering serum cho-
olesterol slowed Alzheimer’s progression.

Dr. Sparks’ study was funded by the In-
stitute for the Study of Aging and by Pfar-
er Inc.

CIs Underused in
Moderate Alzheimer’s

BY SALLY KOCH KUBETIN
Publication Editor

TORONTO — Neurologists are more likely than primary care physicians or psy-
chiatrists to prescribe a cholinesterase inhibitor for a patient with mild to moder-
ate Alzheimer’s disease, but even neurologists fall short of meeting goals in clinical guidelines, Daniel L. Mur-
man, M.D., said at the annual meeting of the American Neurological Association.

The AAN’s evidence-based guidelines on management of patients with dementia call for physicians caring for ambula-
tory patients with mild to moderate dementia to consid-
er using a cholinesterase in-
hibitor (CI) where appropriate, said Dr. Murman of the University of Nebras-
ka, Omaha.

Dr. Murman and his associ-
ates reviewed office visit data from the National Ambulatory Medical Care Survey of officebased non-federally employed physicians. They focused on office visits made in 1993-2001 with the ICD-9 codes 331.0 (Alzheimer’s disease), 290.2 (se-
nile dementia with delusion or dementia), and 290.3 (senile dementia with delirium). Be-
cause the patients were ambula-
tory, their dementia was pre-
sumed to be mild to moderate. A total of 700,000 office vis-
its were made by the study population for Alzheimer’s dis-
ease and senile dementia dur-

Alzheimer’s Cognitive, Behavioral Symptoms
May Respond Differentially to Donepezil

BY BRUCE JANCIN
Denver Bureau

ORLANDO, Fla. — Alz-
heimer’s disease patients who don’t obtain clear-cut cognitive benefits with donepezil nonetheless often experience significant improvement in behavioral symp-
ptoms. The dementia, Ralf Ihl, M.D., said at Wonca 2004, the conference of the World Organiza-
tion of Family Do-
tors.

“Behavioral symptoms should be considered an eval-
uation treatment re-
spose in patients with mild to moderate Alzheimer’s disease. It may require the need for more than one visit to find out if the outcome is positive,” added Dr. Ihl, a psych-
iatrist at the University of Düs-
seldorf (Germany) and president of the European Association of Geriatric Psychiatry.

The often-divergent cognitive and behavioral responses to donepezil therapy were high-
lighted in the Arcept Washout and Rechallenge (AWARE) study, a Pfizer-sponsored randomized clinical trial conducted in eight European nations and the United States.

AWARE had a three-phase de-
sign. In phase I, 1,812 patients with mild to moderate Alzheimer’s disease received 24 weeks of open-label donepezil at 10 mg/day. During this phase, 193 patients withdrew from the study due to side effects and vari-
ious other reasons.

Of the 619 patients who com-
pleted phase I, 68.8% showed clear benefit in cognitive symp-
toms as defined by improvement on the Mini-Mental State Exam-
nination (MMSE) or physician global assessment. At that point their participation in the trial was over. Phase II and III of AWARE were reserved for the 31.2% of patients who didn’t show cognitive im-
provement in phase I.

Phase II was a double-blind study in which patients were ran-
domized to receive donepezil or placebo for 12 weeks. In phase III, everyone who participated in phase II was placed on donepezil for 12 weeks of sin-
gle-blind therapy.

Behavioral symptoms were as-
sessed using the Neuropsychiatric Inventory (NPI). At the close of the double-blind phase II of AWARE, patients in the donepezil arm showed a significant 28.5 point improvement on the NPI, while those assigned to placebo displayed a 0.76-point worsening. The greatest im-
provement with the cholin-
esterase inhibitor was seen in the depression/dysphoria section of the NPI.

The improvement in behav-
ioral symptoms seen with donepezil in phase II occurred in patients who simultaneously ex-
perted cognitive decline as well as in those who remained cognitively stable or showed cog-
nitive improvement.

“This shows those parameters are not really parallel during the course of the disease,” the psy-
chiatrist observed.

In phase III, patients who had been on donepezil throughout the AWARE trial showed continued behavioral improvement. However, patients who had been on placebo in phase II showed an attenuated improvement in be-
havioral symptoms in phase III.

“This shows something that many general practitioners already feel: If you interrupt treat-
ment with a drug against de-
mentia you lose something—and you can’t win it back later even if you bring in the drug once more,” Dr. Ihl said.

He noted that in 1906 when Alois Alzheimer first described the disease that bears his name, the physician stressed that the symptoms of the dementia in-
clude not only cognitive but also behavioral and functional prob-
lems that worsen with time.

“Relevant outcomes in Alzheimer’s disease include all the above cognitive and functional capac-
ities, behavioral problems, quali-
ity of life, resource utilization. They all relate to an increased burden. It’s not sufficient to look only at cognitive decline. You also have to look at other symptoms where there could be significant benefit,” he said.

IHL

Donepezil lessened behavior problems in patients with stable or declining cognition.

DR. IHL

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