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Oral Resveratrol Stabilizes Amyloid in Alzheimer's

Daniel M. Keller, PhD | November 28, 2014

PHILADELPHIA, Pennsylvania — High-dose oral resveratrol (RES) administration stabilized levels of amyloid-beta 40 (Aβ40) in cerebrospinal fluid (CSF) and plasma compared with placebo in patients with mild to moderate Alzheimer's disease (AD), a phase 2 study shows.

"We found that oral resveratrol and its major metabolites penetrate the blood–brain barrier and seemed to have [central nervous system (CNS)] actions at nanomolar concentrations," said lead author R. Scott Turner, MD, PhD, professor of neurology and director of the Memory Disorders Program at Georgetown University in Washington, DC.

"Based on its safety and tolerability and CNS penetration and effects on biomarkers, we might consider further studies on resveratrol, or perhaps synthetic, more bioavailable compounds that mimic the actions of resveratrol," Dr Turner concluded.

The findings were reported here at the 7th Clinical Trials Conference on Alzheimer's Disease (CTAD).

Multicenter Trial

Animal studies have shown that RES, a compound found in grapes, wine, and chocolate, decreases age-dependent cognitive decline as well as neuropathologies in models of Alzheimer's disease and other neurodegenerative conditions.

In the phase 2, double-blind, multicenter, 12-month trial, participants were randomly assigned to receive either oral RES 500 mg once daily (N = 64), escalating to 1000 mg twice daily at 13-week intervals, or matching placebo (n = 55). RES was added onto approved drugs for AD.

Patients had mild to moderate AD with Mini Mental State Examination scores of 14 to 26. At baseline, the only significant difference between the RES and placebo groups was that the patients receiving RES had a shorter duration of AD (mean, 3.9 vs 5.5 years; $P < .001$).

The RES group also tended to be younger (mean, 69.8 vs 73 years; $P = .07$). All cognitive test and performance scores were similar, as were brain volume measurements and CSF and plasma Aβ40 levels.

Pharmacokinetic studies showed that RES and its major metabolites crossed the blood–brain barrier and were found in CSF, as well as in plasma. RES had a plasma t_{max} of 90 minutes and a $t_{1/2}$ of 906 minutes.

RES treatment altered Aβ40 levels in CSF and plasma and was associated with a loss of brain volume and an increase in ventricular volume, possibly explained by reduced edema and inflammation.

Table. Resveratrol Effect on Biomarkers and Brain Volume

Endpoint	Resveratrol, %	Placebo, %	*P* value
CSF Aβ40	−1	−14	.002
Plasma Aβ40	−6	−20	.024
Change in brain volume	−3	−1	.025
Change in ventricular volume	33	27	.049

RES had no effect on Aβ42 in CSF or plasma, CSF tau or phospho-tau-181, hippocampal volume, or entorhinal cortex thickness, all of which were prespecified primary outcomes of the trial.

Secondary outcomes of Clinical Dementia Rating, Alzheimer's Disease Assessment Scale-cognitive subscale, Mini Mental State Examination, or the Neuropsychiatric Inventory were not affected by RES, and neither were glucose and insulin metabolism, including oral glucose tolerance tests.

Resveratrol Well Tolerated

Of the 64 participants randomly assigned to RES, 56 completed the study, which was equivalent to study completion in the placebo group (48 of 55 participants).

The major adverse effects occurring more frequently with RES were nausea (14 when receiving RES vs 5 when receiving placebo) and diarrhea (26 when receiving RES vs 7 when receiving placebo).

The prevalence of serious adverse events was similar for the two groups (20.3% for RES vs 18.2% for placebo; $P = .8$). Three deaths occurred: one in the active treatment group and two in the placebo group. None of the deaths was related to study procedures or the drug.

Neoplasms were more frequent in the placebo group (seven cancers in six participants: three malignant melanomas, two squamous cell carcinomas, one basal cell carcinoma, and one malignant glioma) and were rare in the RES group (one bladder cancer; $P = .048$ for all neoplasms in the RES group vs placebo). Other adverse events were similar between the two groups.

Eleven patients with RES lost weight compared with none in the placebo group ($P = .049$). Most of the weight change occurred after week 26. By week 52, the RES group had lost about 0.9 kg compared with baseline, and the placebo group had gained about 0.5 kg ($P = .047$).

James Hendrix, PhD, director of global science initiatives at the Alzheimer's Association in Chicago, Illinois, commented to *Medscape Medical News* that the study showed "some signal," in that oral RES was associated with a stabilization of Aβ levels in the CSF.

"You didn't see the change that you would normally see in Alzheimer's disease, so that is a positive signal, but again, it calls for more research," he said.

He noted that the mechanism of the RES effects is not clear at this point. "How it's engaging with the target specifically, it's difficult to say for sure unless you can do more detailed studies."

The trial was funded by the National Institute on Aging. Resveratrol was supplied by Aptuit Laurus (now Catalent). Dr Turner and Dr Hendrix have disclosed no relevant financial relationships.

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