

A Randomized, Double-Blind, Placebo-Controlled Trial of Simvastatin to Treat Alzheimer Disease

Objective:

- To determine if the lipid-lowering agent simvastatin slows the progression of symptoms in Alzheimer's Disease (AD)

Methods:

- **Design:** Prospective, open-label, multi-center, double-blind, placebo-controlled parallel trial
- **Inclusion criteria:** Age older than 50 years, Mini Mental State Examination (MMSE) score within the range of 12 to 26
- **Exclusion criteria:** Individuals with other neurologic or psychiatric diagnosis that could interfere with cognitive function, taking lipid-lowering drugs, or if they required cholesterol-lowering treatment as defined by ATP III guidelines, LDL < 80, triglycerides > 500, recently taken drugs with significant central anticholinergic effects, sedatives, antiparkinsonian medications, or any investigational treatment for AD, medications that are specifically contraindicated with simvastatin as well as those that could interact with CYP3A4
- **Drug regimen:** For the first six weeks, each patient received either 20 mg of simvastatin or placebo. The dose was increased to 40 mg simvastatin for the active drug or identical placebo for the remainder of the 18-month study
- **Primary Outcome Measures:** The rate of change on the cognitive portion of the ADAS (ADAS-Cog) score
- **Secondary Outcome Measures:** ADCS-CGIC, MMSE, Dependence Scale, ADCS-ADL, NPI, Maze A2, Number Cancellation, Delayed Word Recall, QOL, and ADCS-RUI
- **Safety Outcome Measures:** Reporting of any adverse events, laboratory abnormalities, or endorsement of items from a "symptom checklist" which directly inquired about known side effects of the drug with specific queries for muscle pain, tenderness, or weakness.
- **Laboratory Evaluations:** APOE genotyping, lipid levels, liver function tests (especially AST and ALT), and CRP
- **Power:** With a dropout rate estimated at 30%, α set at 0.05, and a sample of 400, there was 80% power to see a 20% difference in drugs vs. placebo rate change.
- **Data Handling:** The primary analysis was an intent-to-treat analysis. All available ADAS-Cog assessments were used in the analysis for subjects who discontinued medication but agreed to be followed. In addition to ITT analysis, both a completers and compliers analyses were conducted.

Results:

- In the treatment group, 145 patients completed month 18 on medication and 3 patients completed month 18 of medication. In the placebo group, 152 patients completed month 18 on medication and 4 patients completed month 18 on medication.
- **Primary Outcome Measures:** In the primary analysis, the ADAS-Cog score did not differ between treatment groups ($p=0.25$; 95% CI -0.0462 to 0.1680)
- **Secondary Outcome Measures:** There were no significant differences between groups in secondary outcomes.
- **Safety Outcome Measures:** The number of patients with one or more adverse events in the placebo group did not differ ($p=0.30$). The groups did not differ in the number of subjects

with serious adverse events ($p=0.91$), the number of subjects with serious adverse events requiring hospitalization ($p=0.52$), and the number of deaths ($p=0.29$).

- **Author's Conclusions:** Simvastatin had no benefit on the progression of symptoms in individuals with mild to moderate AD despite significant lowering of cholesterol.

Strengths:

- Double-blind, placebo-controlled, parallel study design
- Appropriate dosage and dosage titrations based on cholesterol lowering effects
- Appropriate monitoring for known side effects of the study medication
- Exclusion of medications that interact with the study medication

Limitations:

- Concomitant use of anti-dementia medication
- No control over patient life factors (living conditions, family support) which may affect quality of life
- Inability to extrapolate data to patients with abnormal lipid levels
- Subjective nature of study outcome measurements
- No data provided to account for adherence

Conclusion:

- The role of simvastatin seems limited in slowing the progression of AD symptoms. I think research is warranted in patients who are treated with cholesterol-lowering medication and their rate of AD development.

References:

Sano, M., Bell, K. L., Galasko, D., Galvin, J. E., Thomas, R. G., and van Dyck, C. H. "A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease." *Neurology*. 2011; 77 (6): 556-63.

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