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Clinical Effects of Oral Tramiprosate in APOE4/4 Homozygous Patients with Mild Alzheimer's Disease Suggest Disease Modification

M.N. Sabbagh

Department of Neurology, Barrow Neurological Institute, Phoenix, Arizona, USA

Abushakra and colleagues (1) report on the effects of oral tramiprosate on apolipoprotein E (APOE) ε4 allele (APOE4) homozygotes. Tramiprosate is an oral amyloid anti-aggregation agent that reduces oligomer formation and fibrillar (plaque) amyloid deposition in transgenic animal models (1–4). Tramiprosate has been shown to inhibit β-amyloid (Aβ) fibrillation and to reduce soluble Aβ. It prevents Aβ formation and deposition by interfering with glycosaminoglycans. It has also been reported to inhibit the inflammatory response. More recently, tramiprosate has been shown to modulate "conformational flexibility of amyloid beta Aβ42, leading to the prevention of oligomer seed formation and thus aggregation" (4).

Phase 2 studies of tramiprosate showed promising data, with evidence of stabilization. Tramiprosate was then evaluated in two 78-week phase 3 trials in patients with mild to moderate Alzheimer's disease (AD). However, the results of the North American trial, which became available in 2007, did not show efficacy in the overall study population (5).

The present report is a substudy of that primary analysis. In the substudy, APOE4 homozygotes were selected. The substudy reports the results from the North American and European Union studies of 2 doses (tramiprosate 100 mg twice daily and 150 mg twice daily) and matching placebo in each study. The APOE4/4 sample comprised 257 subjects. In the mild subgroup identified using the Mini-Mental State Examination (MMSE), tramiprosate proved to be significantly superior to placebo at weeks 52, 65, and 78 ($p \leq 0.01$), as indicated by Alzheimer's Disease Assessment Scale (ADAS) scores. It proved to have statistically significant benefit ($p < 0.05$) at weeks 52, 65, and 78 as indicated by Clinical Dementia Rating (CDR) scale scores, and it proved to be of some benefit at week 78 as indicated by Disability Assessment for Dementia (DAD) scale scores. These data suggest a pharmacogenomically driven effect in a subcohort of AD.

Corresponding Author: Marwan Noel Sabbagh MD, FAAN, c/o Neuroscience Publications; Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, 350 W. Thomas Rd., Phoenix, AZ 85013; Tel: 602.406.3593; Fax: 602.406.4104; Neuropub@barrowneuro.org.

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There are several takeaways here. First, there might be a time when subjects who are likely to benefit from a medication will be selected on an a priori basis. The general finding in previous AD trials has been that, although only a fraction of the treated group responds to the medication, this response drives the entire effect. If the effect in the responders is too weak, then the lack of effect in the non-responders dilutes the effect in the responders.

Second, this study is not the first to indicate differential effects of treatment in APOE4 carriers and non-APOE4 carriers. Previous studies of donepezil produced demonstrable evidence of preferential treatment effects in APOE4 carriers compared to the effects in non-APOE4 carriers (6). Alternatively, some studies have stratified risk on the basis of APOE carrier status, with the most striking example being the phase 3 clinical trials of bapineuzumab (7).

Third, AD in APOE4 homozygotes tends to progress more rapidly than in non-APOE4 carriers, making it possible to clearly identify treatment responses when they occur. This finding suggests the likelihood of different treatment responses and different adverse effects on the basis of the APOE4 carrier status of each individual. Thus, the robustness of the treatment response of APOE4 homozygotes to tramiprosate should not come as a surprise because tramiprosate targets Aβ.

Unfortunately, a post hoc analysis will warrant calls to reproduce these data in yet another phase 3 randomized clinical trial. APOE4 homozygotes represent only 2% of the population, and only 20% of the AD cohorts in clinical trials, which makes it costly and time-consuming to try to reproduce these data. Alternative considerations might include rendering a study to identify the effects of tramiprosate on biomarkers (e.g., as shown by positron emission tomography to identify Aβ in the brain and by examination of cerebrospinal fluid to identify Aβ42/total tau) in APOE4 homozygotes.

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