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TRIAL WATCH

Phase III trial of anti-tau drug generates mixed messages

The tau aggregation inhibitor leuco-methylthioninium-bis(hydroxymethanesulfonate) (LMTM) provided no overall benefits in patients with mild to moderate Alzheimer disease (AD), according to phase III trial data reported at the 2016 Alzheimer's Association International Conference (AAIC 16) in Toronto, Canada (24–28 July 2016). A subgroup analysis, however, hinted at slowing of the disease process in patients who were not receiving standard drug therapy for AD.

The double-blind, placebo-controlled trial recruited 891 individuals with probable AD, 85% of whom were already taking approved AD treatments. The participants were randomly assigned in a 3:3:4 ratio to receive LMTM at 150 mg or 250 mg daily, or a placebo consisting of 8 mg LMTM daily. Administration of a minimal dose of LMTM to the placebo group was necessary to maintain blinding, as the drug — a derivative of methylene blue — turns the urine blue.

Over the 15-month study period, neither of the LMTM treatment groups showed any difference from the placebo group with regard to the primary efficacy outcome, namely, change from baseline on standard cognitive and functional measures. In addition, rates of brain atrophy, as measured by MRI, were similar among the three groups.

In a pre-planned subgroup analysis, participants who received LMTM as monotherapy — that is, those who were not on AD drug therapy at the start of the trial — seemed to exhibit significant slowing of cognitive decline and brain atrophy. However, these individuals were compared with the entire placebo group rather than other drug-naive patients, and this lack of genuinely comparable controls could have created a false impression of the drug's efficacy.

The failure of the drug to meet the primary end point did not prevent the trial from being hailed a success in some quarters. Posting on Twitter, physician and science writer Ben Goldacre noted a curious UK–US divide in terms of press coverage. The UK media carried largely positive headlines, including "New drug slows Alzheimer's progress, research reveals" (*Mail Online*) and "Breakthrough as scientists create first drug to halt Alzheimer's disease" (*The Telegraph*). By contrast, US news outlets were more circumspect, with headlines such as "Alzheimer's drug LMTX falters in final stage of trials" (*The New York Times*) and "Testing of new Alzheimer's drug disappoints, but it's not all bad news" (*CNN*). "This randomized controlled trial actually had a negative result," wrote Goldacre. "UK coverage of this trial … has been criminally misleading … like a game of Bad Science Bingo."

Clinical neurologist David Knopman from the Mayo Clinic, who was not involved in the trial, expressed disappointment at the results. "The only thing that really counts is the primary outcome that is prespecified," he said. "The secondary results are interesting, but secondary analyses are fraught with difficulty." He also pointed out that in North America, few people with AD are not receiving standard care. Consequently, the extent to which the subgroup data can be generalized to other populations is likely to be limited.

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