Alzheimer's Disease Drug Development Targets Disease Modification

BY MITCHEL L. ZOLER

WASHINGTON — Finding a drug therapy for patients with Alzheimer's disease that not only improves symptoms but also slows or stops the underlying disease process and results in disease modification will be a major challenge.

Disease modification "indicates the drug is attacking the underlying biology of the disease. The medications we have now affect only symptoms and are palliative," David S. Knopman, MD, said in an interview during the Alzheimer's Association International Conference 2015.

Designing trials capable of identifying disease-modifying drugs "turns out to be very challenging. In principle, a drug with disease-modifying effects would have bigger and more enduring effects, could be started earlier in the disease, and would ultimately be of greater benefit to patients and to society," said Dr. Knopman, a professor of neurology at the Mayo Clinic in Rochester, MN. He participated in a session at the meeting focused on the potential design of trials that could test a drug's disease-modifying effect.

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Delayed Start

The most likely design that researchers seem ready to use is a "delayed-start" trial, in which placebo-treated patients who serve as controls in the initial, blinded, and randomized phase of an efficacy trial then cross over to open-label treatment once the first segment primary-endpoint stage is finished. In most trials "the open-label, long-term extension will occur anyway," so adding a delayed-start element following the end of an efficacy trial "does not add a lot of complication to the design," he said.

Two factors make a delayed-start analysis challenging. First, the drug needs to show efficacy during the initial, double-blinded phase. "Only if you see both a cognitive and some sort of functional-outcome benefit can you engage in the delayed-start analysis, to see if the effect is enduring," Dr. Knopman said. The second limitation is patient dropout. "An open-label, long-term extension over another 1, 2, or 3 years will invariably lead to subjects dropping out because of health issues or social matters and that makes the statistical analysis more complicated." During one trial that was discussed in depth at the session, about 40% of patients who entered the delayed-start phase had left the study by the time this stage finished 2 years later.

FDA Support

Despite these issues, adding a delayed-start phase to drug trials likely will become increasingly common, Dr. Knopman predicted. Drug developers "will probably include this as a secondary analysis because it doesn't add much expense or added burden on participants, so it seems like a win-win." Plus, representatives from the Food and Drug Administration who participated in the session seemed to endorse the general concept, he noted. But the most important caveat remains, he stressed. "You have to first show primary-outcome results. Only then you can talk about disease modification."

The delayed-start trial design was developed by Eli Lilly. Dr. Knopman received an honorarium from Lilly for chairing the data and safety-monitoring committee for two of their trials through 2012, but since then he has not had a financial relationship with the company. He currently is an investigator in a trial sponsored by Lilly. He said he has no other disclosures.

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