Less Stringent Clinical Improvement Standards Proposed for Trials of New Therapies for Early Alzheimer Disease

BY KURT SAMSON

ARTICLE IN BRIEF

At a meeting of Alzheimer disease (AD) investigators and advocates, panelists discussed the challenges of developing meaningful clinical measures and biomarkers for trials of early AD.

ROCKVILLE, MD—The FDA is open to suggestions for less stringent "meaningful clinical improvement" standards for drug trials of new therapies targeting early pathogenic changes in presymptomatic and milder stages of Alzheimer disease.

But what might constitute be an acceptable alternative remains an open question, said Russell Katz, MD, the director of the agency's neurological drug development arm. While the FDA is focused on clinical meaningful improvement (CMI), he said, "we have no *a priori* effect size" for studies on newer drug candidates. Any change, no matter how small, can be included in a global [definition] of clinically meaningful improvement. There is no requirement in the law on minimum effectiveness."

Dr. Katz was one of several panelists participating in the second annual meeting here July 21 sponsored by ACT-AD (Accelerate Cure/Treatments for Alzheimer's Disease), the Alzheimer's Association, and LEAD (Leaders Engaged on Alzheimer's Disease), a consortium of national organizations representing patients, providers, caregivers, consumers, older Americans, researchers and employers seeking to accelerate development of potential cures and treatments for AD.

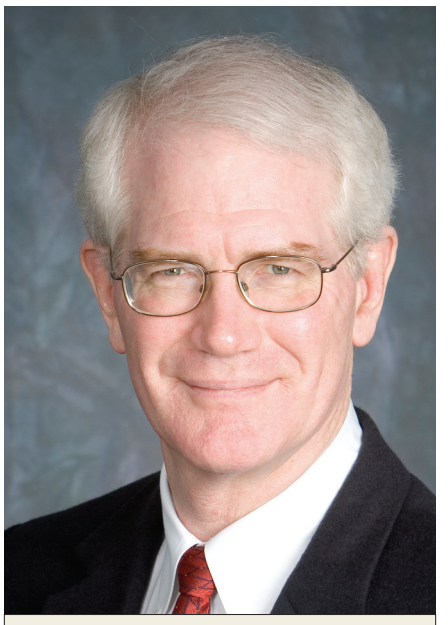
At issue is how best to define CMI in mild cognitive impairment and early AD (MCI-EAD) studies, whether the current standard should apply across all levels of AD severity, whether CMI should be defined separately for different severity levels, and under what circumstances might alteration in rate of cognitive decline, by itself, be considered a clinically meaningful outcome in such studies.

Current CMI standards in trials of drugs for more advanced disease are difficult if not impossible to use in studies of patients with few if any symptoms, said investigators participating in the day's panel meeting.

CLINICAL TRIAL CATCH-22

What is clear, speakers and audience participants emphasized, is that unless the FDA's current CMI definition includes more subtle and gradual stages of patient improvement, it will be difficult to design and attract investment in the next generation of drugs for targeting the biomechanics of early AD.

"There is a general consensus that earlier identification and treatment of AD is important, and the focus is shifting toward treatment in the earlier pre-symptomatic stages," said John D. Morris, MD, the Harvey A. and Dorismae Hacker Friedman Distinguished Professor of Neurology, Professor of Pathology and Immunology, Professor of Physical Therapy, and Professor of Occupational Therapy at Washington University in St. Louis and director of the school's Alzheimer Disease Research Center.



DR. JOHN C. MORRIS: "There is a general consensus that earlier identification and treatment of AD is important, and the focus is shifting toward treatment in the earlier pre-symptomatic stages."

"The rates of cognitive decline are very slow in early disease, and we not only need biomarkers to identify persons with early disease, but also some way of identifying which individuals will deteriorate more quickly."

Biomarkers are increasingly meaningful in detecting AD, and they have been used in research for some time, he noted, but they have yet to be integrated into screening or treatment protocols in early stages of the disease. While cognition remains "the essential biomarker" of AD progression, some global measures of cognitive change are also needed, he said.

Both global and individualized improvement measures are needed, but remain problematic because dementia is a "multidimensional state," even in mild cognitive impairment, noted Kenneth Rockwood, MD, the Kathryn Allen Weldon Chair in Alzheimer Research at Dalhousie University n Halifax, Nova Scotia.

"There's more to MCI than amnesia," he noted. "The idea is that at any given time [patients] are either getting better or worse and the brain is an innocent bystander. But the brain fights back, and patients stabilize or get better for reasons that we don't yet understand.

"What does [improvement] look like?" he asked. "In large population studies, one in seven or eight people stay the same at any given point. The relentless progression model is inaccurate."

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process, although I think the authors were appropriately cautious about the opposite argument," that aggregates are more like bystanders than contributors to the disease.

A major problem in research on ALS and other neurodegenerative diseases is the weak correlation between results in cell and animal models and results in patients. Dr. Benatar said his analysis of the ALS mouse literature led him to conclude that "the data are quite poor, and that there is tremendous publication bias, with negative results not being published."

An additional problem has been that most drugs tried in mice are given before disease onset, rather than once symptoms appear, making the relevance of even a successful result questionable.

"We ultimately settled on arimoclomol because it showed an effect on survival in mice when given after disease onset. But we still recognize we are basing this on a very flawed literature," he said.

Because the preclinical success of arimoclomol was in mice with *SOD1* mutations, and because the disease process in sporadic ALS may not be the same as for *SOD1*-caused ALS, Dr. Benatar's trial is restricted to patients with *SOD1* mutations, specifically those with the fast-progressing A4V mutation. He hopes this will give the highest chance of replicating the good results seen in the mice.

"The real challenge will be recruitment," he said. He calculates there are only about 100 new cases of A4V ALS every year in the US, and he hopes to eventually recruit approximately 50 patients. "That's pretty ambitious."

The trial is taking advantage of the resources from consortium of 80 ALS researchers, "but we are still looking for patients." He is encouraging neurologists who may have appropriate patients to contact him at **sod1@emory.edu**. Genetic testing is being done as part of the trial.

"A successful trial could radically change what happens to patients when they get to the clinic," he said. Currently, few patients receive genetic testing at diagnosis because of the lack of meaningful treatment options based on genetic status. But should the treatment be effective, that would change.

"It also has the potential to change what happens to patients with sporadic ALS," since a small portion of them — perhaps up to 2 percent — also have SOD1 mutations, Dr. Benatar said. •

REFERENCES:

- Prudencio M, Hart PJ, Andersen PM, et al.Variation in aggregation propensities among ALS-associated variants of SOD1: Correlation to human disease. *Hum Mol Genet* 2009; E-pub 2009 May 30.

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A WORKING MODEL?

Just as it does not consider any *a priori* CMI effect size, the FDA does not require that any specific number or type of impairment or improvement scales be used in such studies, Dr. Katz assured the meeting participants.

"We already endorse the use of individual measurements in AD, [but] there are multiple issues from a regulatory point of view."

Citing the experience of the research community and pharmaceutical industry with cholinesterase inhibitors such as donepezil, galantamine, and rivastigmine, the only treatments approved in the US. for AD, Jeffrey Cummings, MD, professor of neurology and psychiatry and director of the Alzheimer Disease Research Center at the David Geffen School of Medicine at the University of California-Los Angeles, said the ADAS-Cog (Alzheimer Disease Assessment Scale-Cognitive) would be one way to evaluate CMI and offers a potential benchmarking mechanism.

He noted that ten major studies using the tool in mild to moderate AD are listed in the Cochrane Collaboration database of published medical research, and from these it can be determined that a 1.4- to 3.9-point improvement on the ADAS-Cog scale is in line with a range of 1.5 to 3.9 points using similar scales, with 1.5 points being the lowest level in cholinesterase inhibitors.

In an 18-month study of r-flurbipro-

fen, or Flurizan, in mild-to moderate AD, a 1.5-point improvement in ADAS-Cog translated into a 25 percent difference between placebo and treated patients at 18 months, with an effect size of 3.3, Dr. Cummings told the audience.

"The European Consortium has recommended a 2 point improvement in ADAS-Cog," he said. "This allows newer agents to compete with generic donepezil after 18 months, but it begins an incremental process. In most of these drugs this is expensive testing, and so far there have only been failures, but I am sure this approach would help initiate development [of new agents.]"

Dr. Katz said that while the FDA does not have set CMI standard for MCI-EAD, the existing global paradigm focuses on a drug's treatment effect and, in the absence of any biomarker with which to measure a drug's effect on early disease, it remains at the forefront of the agency's decision-making.

"In the next phase of drug development with newer drugs for AD we do not know what to expect with regard to treatment effect. But we have an implicit understanding of effect," he said.

"We certainly entertain [meaningful improvement], but in my mind I have to ask, 'how do you measure clinical effectiveness?' The consensus that global changes are the overriding principle is still being endorsed, but we will be willing to look at clinical changes and biomarkers. We would consider big biomarker changes without global change — that would be compelling — but the FDA process and its paradigm starts with some clinical effect." •