In A Game Change, FDA Shifts Criteria for Drug Development to Early-Stage Alzheimer’s Disease

BY MARY BETH NIERENGARTEN

In a move that several leading Alzheimer’s disease (AD) experts welcomed, the Food and Drug Administration (FDA) issued a new guidance document in February refocusing drug development and treatment for Alzheimer’s disease to earlier stages of disease. Among its policy changes, the FDA proposed loosening regulations requiring patients to have both cognitive and functional impairment to be eligible for clinical trials.

The proposed changes, which were explained further in a Mar. 13 paper in the New England Journal of Medicine, reflect an emerging consensus among AD clinicians and investigators that treating patients with primary progressive multiple sclerosis (PPMS) tend to experience more cognitive impairment than patients with relapsing-remitting MS (RRMS), according to a study that involved extensive neuropsychological testing of participants.

Although PPMS is mainly characterized clinically by spinal cord involvement, we observed that cognitive functions are frequently impaired,” Bruno Brochet, MD, a study coauthor told Neurology Today. “Cognitive impairment appears to be more frequent and severe and concerns a wider range of cognitive functions than in relapsing-remitting MS.”

The study, published online Mar. 20 ahead of the print edition of Neurology, was conducted at the University of Bordeaux in France, where Dr. Brochet is a professor of neurology.

Sequestration Means Fewer Medicare Reimbursement Dollars for Neurologists: How to Lessen the Blow

BY SUSAN KREIMER

Each year in her solo neurology practice, Elaine C. Jones, MD, experiences a surge in overhead costs amid a decline in Medicare reimbursement rates. She expects to feel the pinch even more in 2013.

“It is going to be a big hit,” said Dr. Jones of Southern New England Neurology in Bristol, RI. “The bulk of my patients are certainly Medicare patients.”

Automatic across-the-board spending cuts, known as sequestration, have taken hold. Bipartisan majorities in both the Senate and House included the automatic cuts in the Budget Control Act of 2011 as a strategy to force Congress to act on further deficit reduction. When Congress failed to agree on terms in January, it allowed the cuts to take effect.

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ARTICLE IN BRIEF
Investigators reported that patients with primary progressive multiple sclerosis (PPMS) and relapsing-remitting relapsing MS fared worse than healthy controls on cognitive testing; and PPMS patients performed more poorly overall than the matched healthy controls on 16 out of 23 neuropsychological tests, doing worse in almost all domains except visual episodic memory, and visuconstruction.

“The PPMS patients presented with a wide range of cognitive deficits in information processing speed (IPS), attention, working memory, executive function, and verbal episodic memory, whereas the impairments in RRMS were limited to IPS and working memory,” when compared with healthy controls in the study, the researchers pointed out.

STUDY DESIGN
To overcome that shortcoming, the researchers set up a cross-sectional study involving 41 PPMS patients, 60 RRMS patients, and 415 healthy controls. The controls were divided into 20 groups according to age, sex, and education level so there was a good match to each group of MS patients. All participants were at least 18 years old. PPMS patients had symptoms of MS for 14 years or less and RRMS patients had symptoms less than 10 years. Those with psychiatric illnesses, except for stable depressive symptoms, were excluded from the study.

Nearby 88 percent of both the PPMS patients and the RRMS patients were taking disease-modifying drugs at the time of their examination. The average age was 52 for the PPMS patients and just over 37 for the RRMS, and the PPMS group has a greater proportion of women. Disability, as measured by the Expanded Disability Status Scale — 0 to 10, with larger numbers indicating more disability — was 3.5 for the PPMS patients and 1.5 for the RRMS.

All participants underwent a battery of neuropsychological tests that focused on seven cognitive domains: information processing speed, attention, working memory, verbal and visual episodic memory, visuoconstruction, and executive function. Participants were also evaluated for depression, as well as for anxiety and fatigue.

Dr. Petersen acknowledged the risk of giving a drug with potential inflammatory side effects to people without symptoms of the disease, but said some bold and perhaps risky steps are needed. Despite some reservations about the details of the FDA proposal, he emphasized that he agrees with its essence. “I support this approach because there has not been a new drug approved for AD by the FDA in 10 years,” he said adding that perhaps one reason for this could be a flaw in the design of clinical trials that have not permitted intervening earlier in the course of disease.

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These patients represent the majority of patients who develop AD, according to Ronald C. Petersen, MD, professor of neurology and director of the Mayo Alzheimer’s Disease Research Center in Rochester, MN. Although the clinical picture may be similar between people with a genetic mutation for AD and those with the anti-Abeta component, the underlying cause of that clinical picture may be quite different between these groups of patients, he said.

“In all likelihood, there are many other factors that come into play to produce the same clinical picture in a sporadic, nongenetic 85-year-old man with the disease than you see with a 45-year-old man with a genetic mutation with the disease,” he said.

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WHAT ABOUT PATIENT SAFETY?
Just as the FDA is often criticized for moving slowly in approving drugs, an equally strong pressure comes from those who warn about the risks of approving drugs too fast to ensure their safety. Days after publication of the FDA statement, the editorial board of The New York Times editorial board, The New York Times Mar. 17 questioned whether patient safety could be compromised by giving patients with no evidence of disease drugs that may be effective, but have side effects.

Dr. John C. Morris emphasized the need for safety, but noted that by study design, the current prevention trials will only give anti-Abeta therapy to people who are at high risk of developing AD and already have Abeta abnormalities.

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The study authors noted that there is little published research on the cognitive dysfunction that occurs with PPMS as compared with RRMS, and the findings have not all lined up. Some previous studies had methodological flaws because they did not have separate control groups that took into account differences in age, sex, and education levels that occur between the two types of MS, they pointed out.

“Although PPMS is mainly characterized clinically by spinal cord involvement, we observed that cognitive functions are frequently impaired. Cognitive impairment appears to be more frequent and severe and concerns a wider range of cognitive functions than in relapsing-remitting MS,” Dr. Bruno Brochet, said.

Nearly 88 percent of both the PPMS patients and the RRMS patients were taking disease-modifying drugs at the time of their examination.

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vary widely in previous studies (from 7% to 58%),” the researchers wrote. “In our study, 47.4% of patients with PPMS were impaired in at least two cognitive domains.”

RRMS patients had lower scores on five out of 23 tests compared with the healthy controls, lagging behind on tests related to information processing speed, attention, and working memory.

Would greater disability in the PPMS group, as measured by EDSS, explain the differences in cognition? Study authors noted that even after controlling for disability and age, cognitive differences emerged in the PPMS and RRMS patients. The PPMS group did worse than the RRMS group on tests that measure working memory and verbal episodic memory.

The researchers noted that the study had some shortcomings because it did not include MRIs of the participants, an element that would have helped researchers “understand the mechanism underlying the cognitive impairments of patients with these different types of MS.” The researchers could have utilized MRIs to determine if cognitive impairment correlated with brain changes seen on imaging.

“We have previously shown that cognitive impairment may be a marker of diffuse brain abnormalities in early RRMS patients,” they wrote. “The observed group difference in the present study could reflect the fact that PPMS patients have more widespread brain damage; specifically, pathological studies suggest that PPMS patients have diffuse pathology in normal appearing white matter and gray matter injury (both cortical and deep gray matter damage).”

Dr. Brochet said in an e-mail interview that the findings should be useful to clinicians who may be evaluating and counseling MS patients who report cognitive difficulties with work or other activities.

“These results should encourage neurologists to assess cognitive functions in patients with PPMS as part of the clinical workup,” Dr. Brochet said. “Since impairment in processing speed is the most frequent deficit observed in PPMS, focusing on information processing speed could be a good strategy to detect cognitive impairment in routine clinical evaluation. There are a number of interventions that have been evaluated that suggest that cognitive reserve can be improved through increasing physical activity, social interaction and challenging mental activities.”

EXPERTS COMMENT

Lauren Krupp, MD, professor of neurology at Stony Brook University Medical Center in New York, told Neurology Today that the new study was an important addition to the understanding of PPMS, which she said is fortunately getting increasing attention from the scientific community. She said that this MS patient population has been difficult to characterize, in part because the disease is less common than RRMS, and the onset is more subtle and gradual. Patients with PPMS are at great risk in delays in diagnosis and perhaps misdiagnosis.

“It’s harder to make the diagnosis and we don’t have treatments to offer,” she said of PPMS. Sorting out whether cognitive changes are due to the disease itself or in combination with the added effects of aging can also be tough.

“Primary progressive patients tend to be older and those people then are struggling not only from the effects of the disease, but also with decline that can come with aging,” she said.

Dr. Krupp said she was recently awarded a grant from the National MS Society to study whether “cognitive retraining” using computer programs to enhance cognition could be helpful for MS patients, including those with PPMS.

Ralph Benedict, PhD, professor of neurology and psychiatry at University at Buffalo, told Neurology Today that he was somewhat surprised by the findings that patients with PPMS have such a greater extent of cognitive impairment than those with RRMS. “Some studies have reported that, but not to this degree,” he said.

Dr. Benedict, who studies MS, said one of his research aims is to understand grey matter atrophy and how brain changes affect clinical outcomes. He is also interested in the development of good psychometric measures that could be universally used to study cognitive function in MS patients. He noted that different studies use different measures, making comparison of findings difficult.

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