Advances in Imaging Boost Alzheimer's Research

BY MICHELE G. SULLIVAN

FROM THE INTERNATIONAL CONFERENCE ON ALZHEIMER'S DISEASE

A range of new amyloid imaging agents has the potential to improve both the diagnosis of Alzheimer's disease and research protocols into potential Alzheimer's therapies.

Trials of two new ^{18}F imaging compounds have demonstrated the agents' ability to bind to amyloid plaque, revealing their potential to detect the buildup of amyloid over time in patients who develop or have progression of cognitive impairment and to differentiate Alzheimer's disease from other types of dementia.

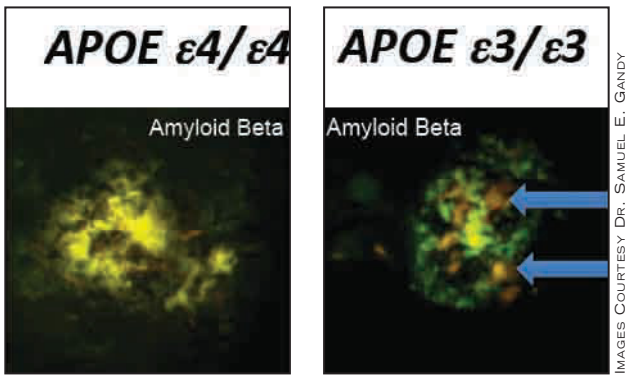
Studies of another class of molecules, called luminescent conjugated oligothiophenes (LCOs), are beginning to show differences in the ways in which amyloid is deposited in the brains of Alzheimer's patients who are homozygous for the apolipoprotein E e4 allele (APOE e4) compared with those who are homozygous for the e3 allele.

Florbetaben and florbetapir are both ^{18}F imaging compounds that bind to amyloid plaque in the human brain. Both have shown promise as agents that might be able to establish a firm diagnosis of the disease, even early in the disease process—allowing for early, more effective treatment, said Dr. Marwan Sabbagh, chief medical and scientific officer at Banner Sun Health Research Institute, Sun City, Ariz.

"The field has been moving much more toward the development of in vivo diagnostic agents that would allow us to make a diagnosis with reasonably good confidence and to move beyond using the autopsy as the gold standard of Alzheimer's diagnosis," he said in an interview. "In the research setting, having a firm diagnosis will allow us to pick subjects for trials on the basis of whether they have amyloid in the brain. Current estimates are that as many as 15% of Alzheimer's trial participants actually don't have amyloid present, which probably contributes a lot of noise to the trials."

Both florbetaben and florbetapir are similar to the Pittsburgh compound B (PiB)—the first compound capable of visualizing amyloid plaques in a living patient during a positron-emission tomography scan. But PiB has a very short half-life, seriously limiting its large-scale clinical applicability, said Dr. Sabbagh.

"PiB PET was a great first step in the realm of amyloid imaging, but its development has been mired by the fact that it's a ^{11}C compound, with a 20-minute half-life. The ^{18}F compounds don't have that concern, and because of that, can be used in a way that is similar to the current fluorodeoxyglucose PET scan that is used to diagnose cancer and other diseases. The ^{18}F amyloid agents are simply replacing fluorodeoxyglucose with another radioisotope. We will be able to use the same technology, just with radiologists who are trained on the new visualizations. But the administration of the imaging won't change the current technology—and that's what is so appealing."



IMAGES COURTESY DR. SAMUEL E. GANDY

Oligothiophenes glow yellow in amyloid from patients with APOE e4/e4, and orange in those with APOE e3/e3.

Florbetapir Amyloid Imaging

Dr. Sabbagh has been an investigator on two florbetapir trials, both of which were presented at the meeting in Honolulu, which this newspaper covered remotely.

In a phase III trial of florbetapir, amyloid burden seen in PET scans highly correlated with plaques seen in the same patients at autopsy. A second study showed that repeated florbetapir amyloid imaging could detect differences in the levels of amyloid binding over time in a group of healthy controls and patients with mild cognitive impairment.

In the end-of-life study, headed by Dr. Christopher Clark of Avid, the tracer was used to examine plaque burden in 35 Alzheimer's patients with less than 6 months to live. After death, brain sections from regions seen as plaque-damaged were examined histopathologically to determine correlation with PET results.

The autopsies showed a strong correlation between amyloid burden and both the visual ratings of the florbetapir PET scans and the patients' mean modified scores on the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery.

The longitudinal follow-up study, conducted by Dr. Reisa Sperling of Brigham and Women's Hospital in Boston, comprised 47 patients with confirmed mild cognitive impairment (MCI) who were matched with 62 elderly healthy controls.

After a neuropsychological testing battery, all of the patients underwent PET imaging with florbetapir. The images were visually scored as amyloid positive or negative by three readers blinded to the diagnoses. Testing 6 and 12 months later included symptom reassessment, the dementia severity rating scale, and informant-based functional assessment.

Images were positive for amyloid in 38% patients with MCI at baseline, compared with 13% of the healthy controls. Florbetapir uptake correlated positively with the dementia severity rating scale in both groups, with higher baseline amyloid related to greater functional impairment at follow-up.

By 1 year, none of the healthy controls had progressed to MCI. However, 4 of the 18 amyloid-positive MCI patients (22%) had progressed to Alzheimer's disease, compared with 1 of the 29 amyloid-negative MCI patients (3%).

Although the results are encouraging, Dr. Sabbagh said, "it's too early to tell if florbetapir can be used as a prognostic agent," as well as a diagnostic agent.

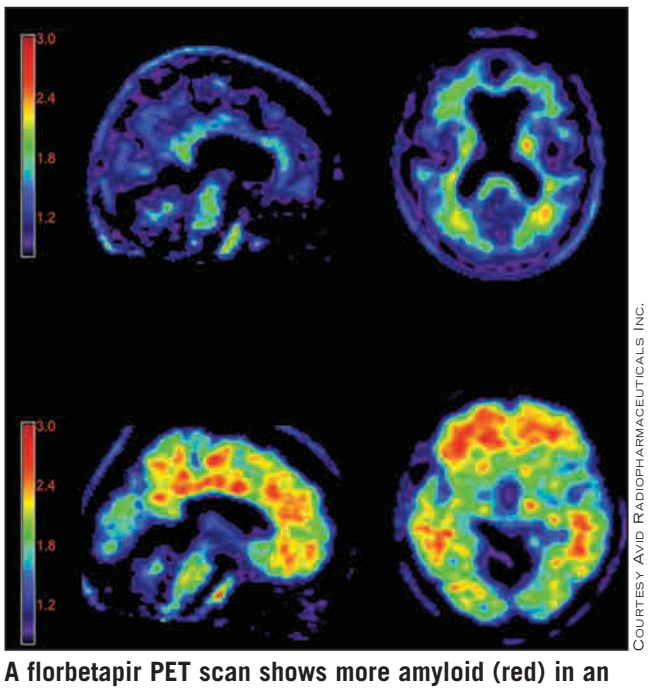
Dr. Sperling and Dr. Sabbagh have received research grants and support from Avid.

Florbetaben Studies

The studies for Bayer's compound, florbetaben, focused on its sensitivity and specificity, and its ability to differentiate Alzheimer's from other forms of dementia.

Dr. Osama Sabri of the University of Leipzig, Germany, lead a phase II trial that comprised 150 subjects imaged with the compound; 81 of these had probable Alzheimer's disease. The PET images were visually rated by three blinded readers.

More than 95% of the images were considered to be of high quality. The investigators found that florbetaben had a sensitivity of 80% and a specificity of 90% for the discrimination of Alzheimer's patients from healthy controls. They also found that the APOE e4 was significantly more common in the amyloid-positive than the amyloid-negative patients (65% vs. 22%, respectively).



COURTESY AVID RADIOPHARMACEUTICALS INC.

A florbetapir PET scan shows more amyloid (red) in an Alzheimer's patient (bottom) than in a healthy volunteer.

"The sensitivity and specificity were reasonably good for this compound," Dr. Sabbagh said.

The differential diagnosis study, lead by Dr. Victor Villemagne of the Austin Hospital, Melbourne, used florbetaben PET imaging in 26 Alzheimer's patients, 11 with frontotemporal lobar degeneration (FTLD), 6 with Lewy body dementia (LBD), and 26 healthy controls.

The Alzheimer's patients showed significantly higher uptake of the compound in neocortical areas compared with all the other groups.

Nearly all of the Alzheimer's patients (96%) showed diffuse cortical uptake, whereas only white matter binding was seen in most of the healthy controls (85%), FTLD patients (91%), and LBD patients (67%).

"This should not be surprising, because frontotemporal dementia is a tauopathy, not related to amyloid, and Lewy body patients and normal controls should not have amyloid in their brain," Dr. Sabbagh said. "It's reasonable to say that this compound has the potential to discriminate one form of cognitive disorder from another."

Both florbetaben studies were sponsored by Bayer Schering Pharma. Dr. Villemagne and Dr. Sabri have both received research grants and support from the company.

Plaque Differences Detected

New agents called luminescent conjugated oligothiophenes (LCOs) are beginning to reveal to scientists how APOE status affects the way in which beta-amyloid protein aggregates in the brain of Alzheimer's patients.

These compounds have shown that Alzheimer's patients with a double copy of APOE e4 develop beta-amyloid aggregates in brain blood vessels that are clearly different in structure or conformation from the aggregates in the brain substance, while in those who are homozygous for the APOE e3 allele, the protein clumps in both the vascular and core structures take on apparently identical conformation, said Dr. Samuel E. Gandy, who serves as associate director of the Alzheimer's Disease Research Center at Mount Sinai School of Medicine, New York.

LCOs intercalate into protein structures and fluoresce different colors depending on the discrete conformational shape they take when encountering different proteins.

When the compounds encounter amyloid plaques, they tend to glow orange; when they encounter neurofibrillary tau tangles, they tend to glow yellowish green.

Dr. Gandy has been an adviser or consultant for Amicus Therapeutics Ltd.; DiaGenic ASA; Elan Pharmaceuticals Inc.; and Johnson & Johnson Pharmaceutical Research & Development, LLC. ■