

Toronto: Last Gift to Science—Hospice Patients Validate Amyloid Ligand

This is Part 3 of a five-part series. See also [Part 1](#), [Part 2](#).

6 May 2010. At present, at least four companies are developing amyloid imaging agents coupled to the radiotracer ¹⁸F rather than ¹¹C. While the original ligand ¹¹C PIB is still considered to be the most sensitive of the amyloid imaging options to date, an ¹⁸F-labeled compound must be had if amyloid imaging is to become widely used in large-scale multicenter drug testing and earlier-stage diagnosis. At the 4th Human Amyloid Imaging Conference, held 9 April 2010 in Toronto, Canada, scientists presented data on three of the ¹⁸F contenders; a fourth was discussed at the 11th International Geneva/Springfield Symposium on Advances in Alzheimer Therapy held earlier this spring in Geneva, Switzerland. Counting by clinical milestones, Avid Radiopharmaceuticals' florbetapir (formerly known as ¹⁸F-AV-45) is arguably furthest ahead in the race to FDA qualification. Having been formally studied in some 270 people to date, it supplies the ADNI-Go study and is the ligand of choice for the ADNI 2 grant. At HAI, **Adam Fleisher** of the Banner Alzheimer's Institute in Phoenix, Arizona, presented an interim analysis of the first six cases of a Phase 3 histopathology validation study that the FDA requires as part of the qualification package for each ligand. Phase 2 results on florbetapir were reported at the 2009 ICAD Conference in Vienna, Austria (see [ARF related ICAD story](#)).

This is a 26-center U.S. study involving 150 adults at the end of their lives. Approximately half have AD; all have fewer than six months to live, many of them in hospice. They undergo a 10-minute florbetapir scan and some neuropsychological testing, if possible, and are then followed until autopsy. The basic idea is to compare the accuracy of a visual rating of florbetapir imaging by three trained readers and a quantitative analysis by SUVR of six brain regions to the participant's subsequent postmortem pathology as measured conventionally by immunohistochemical amyloid burden and CERAD scoring of plaque density. The study was funded by AVID; Fleisher is a site investigator at Banner on this trial, with Banner Sun Health Research Institute acting as the core pathology laboratory. Fleisher reports no personal financial relationship with the company.

The first patient to be autopsied in this study was a 47-year-old woman who met clinical diagnostic criteria for MCI and scored 24 on the MMSE. She had end-stage kidney disease and died 11 days after the scan. She was amyloid-negative on the visual read and by SUVR quantification, and her brain contained no amyloid pathology. Her cognitive impairment might have been a result of her dying from kidney failure, Fleisher speculated. The second patient was an 82-year-old man with a clinical AD diagnosis and an MMSE of 14. He had metastatic prostate cancer and died 53 days after the scan. His brain amyloid was below threshold both by the florbetapir visual read and quantification and by way of postmortem pathology. He did have isolated neurofibrillary tangles in his medial temporal lobes, Fleisher noted. The third patient was a 78-year-old man diagnosed clinically with advanced Parkinson disease dementia (PDD); he was bedridden, rigid, scored 5 on the MMSE, and passed away the day after his florbetapir scan. This man was amyloid-positive by florbetapir imaging, and postmortem pathology yielded an AD diagnosis with plaques, tangles, and diffuse cortical Lewy bodies. The fourth, fifth, and sixth patients, aged 76 to 84, all had clinical diagnoses of AD with MMSE scores of 6 to 0. All died within a month after the scan of their end-stage AD, and all were amyloid-

positive by both imaging measures as well as by both postmortem pathology measures.

A larger sample size is necessary before the investigators can determine how sensitive florbetapir is compared to postmortem pathology, Fleisher said. The common thread so far is that, in every case, the amyloid imaging measure matched up with postmortem pathology, even if those two together contradicted the prior clinical diagnosis. This suggests that florbetapir retention actually measures amyloid pathology, Fleisher said. Others agreed, noting that until now there had been some lingering doubt whether these ligands really “see” amyloid. “But now postmortem validation is coming on a larger scale beyond individual case studies. If it shows, as it did here, that the cases themselves vary greatly but imaging and pathology always correlate, then that counts as proof and hopefully will lead to regulatory approval,” commented **Alexander Drzezga**, a neuroimaging expert at the Technical University in Munich, Germany, who is not involved in these hospice studies.

That the visual read came out in line with the quantitative assessment implies that amyloid imaging eventually may be read rather simply at local PET centers, neurologists’ offices, and in large multicenter drug trials. One worry had been that it might require highly trained, rare specialists or quantitative analysis. This is a priority in implementing any new imaging procedure on a broad basis. “The visual impression of an amyloid PET scan is most important at the sites,” agreed **Osama Sabri** of the University of Leipzig, Germany, who tests a competing ligand in Phase 2 and an ongoing Phase 3 histopathology validation.

Fleisher’s talk generated a fair amount of praise and hallway buzz throughout the day. One point of criticism came up as well. It is that the investigators did not also take an MRI to prove that the anatomic regions seen in the PET scan registered exactly with the areas later studied by postmortem pathology. Some critics pointed out that the spatial resolution of amyloid PET is too low to align regions precisely without an accompanying MRI scan. Others countered that while that is true, hospice studies are ethically sensitive as it is, and lessening the burden on a person who is near death rightly takes precedence. “I would hope that as long as you have global amyloid positivity and an approximate registration, it will prove the point to the FDA well enough,” said Drzezga.

Case-by-case histopathology research is continuing within academic research as well. At HAI, **Val Lowe** from the Mayo Clinic in Rochester, Minnesota, added new examples to the small existing literature ([Ikonomic et al., 2008](#); [Bacsikai et al., 2007](#); [Leinonen et al., 2008](#); [Burack et al., 2010](#); [Cairns et al., 2009](#); [Rosen et al., 2010](#)). Overall, Lowe found increased PIB binding in three people who had been clinically diagnosed as having Alzheimer disease, amnesic mild cognitive impairment (aMCI), and dementia with Lewy bodies (DLB), respectively; all three also had corresponding pathology according to CERAD criteria. A person who died with a clinical diagnosis of non-amnesic MCI and a normal control did not. One of the finer points of this study, though, for example, which kinds of plaques prevailed in the respective cases, Lowe noted seeing considerable variation.—Gabrielle Strobel.

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