Toronto: Sister 18F Ligands Jostle for Primacy

This is Part 4 of a six-part series. See also Part 1, Part 2, Part 3.

7 May 2010. At the 4th Human Amyloid Imaging (HAI) Conference held 9 April 2010 in Toronto, Canada, one 18F amyloid ligand strutted its Phase 3 stuff, while two others flaunted Phase 2 results. A third ligand was fresh in people's memory from a recent presentation of Phase 1 data (see upcoming Part 5 of this series).

The Bayer Healthcare Ligand
Osama Sabri, University of Leipzig, Germany, is the principal investigator of the Phase 2 clinical trial program for Bayer Healthcare's ligand, 18F florbetaben. Bayer funded this study; Sabri has received consulting fees from the company. For those of our esteemed readers who are trying to keep up with the alphabet soup that is amyloid tracer terminology, florbetaben is a stilbene compound formerly known as BAY94-9172 or AV-1/ZK. It differs from Avid's florbetapir (see Part 3 of this series) only by a carbon-to-nitrogen substitution in one position. Bayer Schering Pharma licensed it from AVID and began testing it in single-site studies led by Sabri and by **Chris Rowe** of Austin Health in Melbourne, Australia. In Toronto, Sabri presented a full analysis of an 18-center Phase 2 study conducted in Australia, the U.S., and Europe. It probed florbetaben's ability to distinguish AD from normal in 150 participants aged 55 and older who underwent PET and MRI scans.

Sabri emphasized that this trial's mark of distinction is its combination of assurance that the control participants are indeed cognitively normal (which resulted in a comparatively low amyloid-positive rate in the control group), with external quality control of each image at the Molecular Neuroimaging Institute, a service company in New Haven co-founded by Kenneth Marek and John Seibyl. "Every image was evaluable, we had no dropouts due to quality. That is unusual for an 18-center study," Sabri said.

The sensitivity and specificity with which visual assessment of the scans by three blinded readers replicated the clinical diagnosis served as the primary endpoint of this trial. That's because Bayer intends eventually to market florbetaben as a diagnostic aid and therefore wants it to be clinically practicable on-site, Sabri said. An automated quantification of the amyloid signal served as the secondary endpoint; this was done by obtaining standard uptake value ratios (SUVRs) of volumes of interest derived by gray matter segmentation of the participants' MR scans. The segmentation served to diminish the effect of florbetaben's non-specific white matter binding, Sabri said. As with quality control of the images, the New Haven group performed this quantification as an external site for the entire study.

The primary endpoint came out as 80 percent sensitivity, 90 percent specificity on visual read. For a trial of this size, this is but a small decrement from the higher results of prior single-site studies on florbetaben or smaller multicenter studies with 18F compounds, Sabri emphasized, insisting, "These numbers are great." In this study, the clinical diagnosis served as the standard of truth.

In the secondary endpoint, each of eight regions of interest showed a highly significant difference between the AD patients and healthy volunteers. The posterior cingulate distinguished particularly well, Sabri said.

The groups had some overlap: six healthy volunteers lit up as amyloid-positive and 16 patients with diagnosed AD came out as amyloid-negative. The next study, a Phase 2b, will enroll 270 participants, and a histopathology validation study is also currently underway, Sabri added. For a diagram of this compound's structure and its reported affinity to AD brain homogenate (see ARF related news story).

The GE Healthcare Ligand

Rik Vandenberghe at the University Hospital Leuven, Belgium, presented for the first time the primary outcome analysis of a smaller multicenter Phase 2 trial of an 18F-labeled derivative of PIB called 18F-flutemetamol, formerly known as 18F AH110690. This follows a Phase 1 study with 16 patients (Nelissen et al., 2009). GE Healthcare funds this research.

This trial took place at seven sites in Belgium, Denmark, and Sweden. It enrolled 27 AD patients, 20 people with MCI, 15 cognitively normal controls above the age of 55, and 10 younger than that. Like in the florbetaben trial, the investigators wanted to know primarily how well a visual assessment of the images obtained with this ligand distinguished probable AD from the elderly controls. On this goal, five blinded readers categorized 25 of the 27 as having "raised" uptake, and 14 of the 15 cognitively normal elderly as "normal," yielding a sensitivity and specificity of 93 percent. The raters' independent classifications generally agreed with each other, Vandenberghe said. As in the florbetaben study, the visual read was concordant with a quantitative SUVR analysis. All told, flutemetamol worked in this study; next, an ongoing study is going to calculate how strongly flutemetamol binding predicts AD in an MCI population, Vandenberghe said.

Next, the scientists asked how this compares with PIB, widely seen as the gold standard in amyloid imaging. They ran a small comparison of PIB and flutemetamol. Incidentally, numerous academic investigators over the years have called for side-by-side comparisons of the different amyloid imaging ligands. An AstraZeneca representative casually told this reporter earlier this year that her company was willing to make their compound available for direct comparison, perhaps because it seems promising but is running behind the others at present. But in general, commercial sponsors have shown limited appetite for such an exercise up until now. This small PIB-flutemetamol comparison represents an exception, made easier because GE has also licensed PIB.

In any event, Vandenberghe and colleagues administered both PIB and flutemetamol scans on the same day to 20 AD and 20 MCI patients. Again by visual assessment, the PIB scans were 100 percent concordant with the flutemetamol scans, Vandenberghe told the audience. Both ligands identified all 20 AD and nine of the 20 MCI patients as having raised brain amyloid levels. However, the scientists did not compare the two ligands in the same cognitively normal controls, where subtle differences in their sensitivity might be most likely to show up.

The normal controls in this study received a flutemetamol scan. A small fraction of this group, one out of 15 elderly controls, turned out amyloid-positive than in similar studies with PIB (see Part 2). A larger normal cohort is currently being studied, but Vandenberghe speculated that these differences come down to the cohort. "This is an important question. We find a very high concordance between PIB and flutemetamol.

It does not depend on the ligand; it depends on how the cohort is defined and subjects recruited," Vandenberghe said (see also Part 1 of this series),

In a later discussion about whether 11C PIB still has a place, Vandenberghe noted that his site on occasion had to call back volunteers for a second scan when local production of 11C PIB failed, whereas this snafu did not happen with the 18F compound. "For large multicenter trials, it is simply more practical," he said. For certain research questions, however, scientists generally agreed that PIB still reigns supreme. "For our new program project, we chose PIB because we are looking for very subtle signals. But I am thrilled that the data on the 18F ligands are so concordant, because we will need large primary prevention trials, and they seem comparable and reliable for that," said **Reisa Sperling** of Brigham and Women's Hospital in Boston (see also Sperling talk from a recent conference in Miami Beach, Florida).—Gabrielle Strobel.

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