Launching a new Alzheimer's prevention study

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New diagnostic techniques are giving doctors the ability to recognize clinical signs suggestive of Alzheimer's disease as much as 15 years before symptoms appear. A new drug trial is testing whether the onset of disease can be prevented or delayed. Butler Hospital, one of 60 test sites, has enrolled the study's first patient. Dr. Stephen Salloway discusses the study and new efforts to combat Alzheimer's.

On June 9, Butler Hospital kicked off the international A4 Study, an Alzheimer's disease drug trial in which doctors at 60 sites will test whether a drug can prevent or slow the onset of Alzheimer's disease in people who are building up protein plaques in the brain. Dr. Stephen Salloway, professor of neurology in the Warren Alpert Medical School, is leading the trial at Butler Hospital, while Dr. Brian Ott is leading it at Rhode Island Hospital.

Salloway spoke with David Orenstein about A4's emphasis on Alzheimer's prevention, how Butler ended up leading off with the trial's first patient, and the many other things he's working on to combat the pervasive and devastating disease.

What's the premise of the A4 study?

The A4 trial is really a landmark study that builds on fundamental work to change our view about Alzheimer's disease. It's one of our top three public health problems and one that could break the bank of our medical

care system.

I think this is a game changer for Alzheimer's in that it puts the focus on Alzheimer's prevention—on a par with other major diseases like cancer, heart disease, and HIV.

Until recently you had to have significant cognitive impairment before you could be diagnosed. With advances in molecular imaging and diagnostics we've been able to detect that the changes in Alzheimer's occur in the brain at least 15 years before the symptoms. Using amyloid positron emission tomography (PET), we can now detect people at risk and try to slow down the disease process.

The study is designed for people 65-85, who are cognitively normal but have amyloid PET scans showing that they are building up amyloid plaques. They will either receive a monoclonal antibody against amyloid or placebo monthly for three years with the goal of delaying cognitive impairment.

A4 is a platform. This is the first drug we're testing but there is a plan for A5, A6, and combination treatments. I think this strategy will work eventually. Whether this particular drug is a single or a home run or whatever remains to be seen.

How does the drug work?

The drug, solaneuzumab, is a form of immunotherapy. It's a monoclonal antibody that's active against the toxic form of amyloid called A-beta 42 that builds up in the plaques. The drug targets the soluble form of A-beta.

We don't know exactly how it works, but it binds to amyloid in the bloodstream. There is a dynamic equilibrium between amyloid in the

brain and amyloid in the blood. When you bind it in the blood you actually pull some amyloid out of the brain. That's called "the sink hypothesis."

[In a previous study] the primary outcomes were negative in patients with mild to moderate Alzheimer's and dementia. When they looked at a secondary analysis in the mild group only, there appeared to be some slowing in the rate of cognitive decline, or at least a hint of it. They did change amyloid in the bloodstream and they did change some amyloid in the spinal fluid but looking at total brain amyloid there was no change. So there wasn't a clear biomarker signal. It remains to be seen.

But it was very safe and well-tolerated. Remember, these are normal people in the community. These are not patients coming for care. We wouldn't want to expose healthy people to a high risk without a clear benefit.

How did Butler Hospital become the first site to launch?

We feel very privileged to be launching this trial because of the significance of the project.

The staff—our lead coordinator Melanie Faust and the other staff working with her, such as Diane Monast—have been terrific. The A4 team gracefully surmounted many administrative hurdles.

The Butler system is still pretty small, so you can talk to people to solve problems quickly. We have a good relationship with the research staff and IRB at Rhode Island Hospital where the PET imaging and the MRI is going to be done. Everybody cooperated.

It turned out that our first patient had a positive scan. He's a horticulturalist so he's a science-minded person, a progressive, forward-thinking person.

Is this the first Alzheimer's prevention trial?

There have been Alzheimer's prevention trials, like using gingko biloba or one based on the circumstantial evidence retrospectively that there were some people who take nonsteroidal anti-inflammatory drugs who were less likely to get Alzheimer's, so let's try NSAIDs in normal elderly people.

But this is the first really targeted molecular immunotherapy-based approach. It's more of a rational pharmacology: We know what the pathology is so let's target the pathology early. That's what's so exciting about this. We're not just taking something off the shelf and saying, "Oh gee, maybe this will work."

What else are you working on?

We are very excited that next week we will be initiating new molecular imaging called tau PET [tau proteins are also implicated in Alzheimer's]. We have three tracers that have been approved to see amyloid buildup but we are testing the first tracer to see the tau buildup. That looks very promising from the preliminary data.

That's a big advance because previously we had to wait until people passed away and look under the microscope at their brain, but now we can get that same type of information safely from these brain scans. As more tau agents come into treatment and testing, we'll be able to monitor how effective they are against tau.

We're also testing deep brain stimulation, which is a treatment approved for Parkinson's disease. We're testing it in the cognitive circuits in the brain to try to enhance memory in people with Alzheimer's. It's another partnership. The patients are seen here at Butler but the surgery and the imaging are being done over at Rhode Island Hospital.

We are also testing other amyloid-based treatments, beta secretase inhibitors or other monoclonal antibodies. These are for patients with either mild cognitive impairment or mild to moderate dementia.

And we're doing another prevention trial in family members with autosomal dominant Alzheimer's. The family carries a mutation that causes early onset of Alzheimer's around age 50. We are treating them 15 years before the expected onset to 10 years after. We're testing solaneuzumab plus another monoclonal antibody, gantenerumab, to try to delay cognitive decline.

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