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Alzheimer's Research: Opening the Blood-Brain Barrier with Aducanumab and Focused Ultrasound

Dr. Wilner:
Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner, and joining me today to discuss his research on combining aducanumab with focused ultrasound to open the blood-brain barrier in people with Alzheimer's disease is Dr. Marc Haut. Dr. Haut is the Director of the Rockefeller Neuroscience Institute's Memory Health Clinic at West Virginia University in Morgantown.

Dr. Haut, great to have you with us today.

Dr. Haut:
Thank you very much for having me.

Dr. Wilner:
Let's start with some background. First, a word about aducanumab. It's a new FDA treatment for Alzheimer's disease, and I haven't had an opportunity to use it yet. How is it supposed to work?

Dr. Haut:
So aducanumab is the first drug that was approved by the FDA that's a disease-altering medicine for Alzheimer's, and what it does specifically is it's a monoclonal antibody for amyloid, so it's an antibody made up in the lab that targets amyloid and that gets your own immune system to break up the amyloid. For 30 years or so, people have been trying to come up with a way to clear the amyloid to see if it made a difference in clinical outcome. Aducanumab is the first one that, according to some people, safely lowered the amount of amyloid and may have had a clinical signal. It was first approved by the FDA without full approval based upon its ability to lower amyloid alone as a biomarker. And so it was exciting to many people because they had been after that for 30 years. It works by infusion, and you get an infusion every four weeks because at that four-week mark, the antibody level starts to drop, and you want it constant to keep going after that amyloid and clear it out.

Dr. Wilner:
So where does ultrasound come in?

Dr. Haut:
So ultrasound, as most people know in medicine, is typically used as an imaging tool. In this case, "focused" is the keyword. So imagine yourself with the hemisphere array, and inside that hemisphere is a thousand transducers, each of which can emit a single soundwave to a precision of one millimeter. And so it's in some respects like radiosurgery or gamma knife in that you can send the soundwaves from many, many different locations, so no one track of tissue gets affected by it. Now in this case, you're having the soundwaves converge at the same time in a particular location to open the blood-brain barrier. To do this, you also administer microbubbles, the same bubbles that are used for a cardiac echo. Those are injected, they circulate, and when they're in the vessels in the brain and the soundwaves hit them, they jiggle and expand and open up the tight junctions that make up the blood-brain barrier, so it is that jiggling action that expands the barrier and then allows it to contract. So in this case, ultrasound is used as a device to manipulate the blood-brain barrier.

Dr. Wilner:
So how did you explore this combination in your study?

Dr. Haut:
Well, to begin with, we did initial studies with just opening the blood-brain barrier with focused ultrasound. It had been done up at the

University of Toronto with Alzheimer's about six years ago, and then five years ago, we applied it here in the US. We opened the barrier, and we made sure it closed back up relatively quickly and safely, with the goal being that once we demonstrated this, we would then introduce an agent that could penetrate the brain—and in this case, it was aducanumab, the monoclonal antibody. So five years' worth of work to open the barrier safely and then to get the monoclonal antibody into that very specific location where we opened the barrier and determine its safety, really.

Dr. Wilner:
So was this a double-blind study with some Alzheimer patients getting ultrasound and then some not getting ultrasound, and they're all getting aducanumab? What did you do?

Dr. Haut:
So this is a phase 1 study at best. So it was three individuals, and it was all about safety and feasibility, really. We did not blind this in any way. They knew they were getting the intervention, including the aducanumab, and we were really just making sure we could do it safely without adverse events from combining these two things that are done, typically, separately. We just followed the prescribing guidelines from the FDA. So a person would come in, they'd get their infusion, and we would watch them for two hours to make sure they didn't have any infusion-related reactions, and then we would open the blood-brain barrier using the focused ultrasound, and then we would monitor them for 23 hours under observation in the hospital. If they're good—they all were—then they would be discharged from the observation, they'd get another MRI scan to make sure that the barrier was closed, and then we'd check them at one week or one day and then one week and then before the next infusion, which would be a month later.

Dr. Wilner:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner, and I'm speaking with Dr. Marc Haut about his study that focused on opening the blood-brain barrier in patients with Alzheimer's disease by combining aducanumab and focused ultrasound.

Okay, Dr. Haut, so for these three patients, you opened the blood-brain barrier; they got their regular treatment with aducanumab. What did you find?

Dr. Haut:
So if I could just clarify a touch, they got their aducanumab, and then we opened the blood-brain barrier. So we knew the drug was on board, we opened the barrier, and then, periodically, we would do amyloid PET scan. So we had a baseline amyloid PET scan, and then we would repeat that over the six months of the trial. So we opened the blood-brain barrier six times on each patient while they were getting their standard administration of aducanumab.

So the first time that we did it was in a very small area of the brain. It was less than 10cc, in the right frontal lobe to be very careful and safe, to make sure there wasn't exaggerated hemorrhaging or bleeding or anything like that. And then with the second patient, we were able to open 20cc, and the fourth patient 40cc, and we would do that repeatedly over six months. If you don't know, aducanumab's dosing is ramped up over six months. For the first two months, you get 1 mg/kg. At months three and four, you get 3 mg/kg and then 6 mg/kg, and then we stop before we even got to the highest dose, which is 10 mg/kg, so we didn't even give the highest dose. And what we found was about a 50 percent overall reduction in the target areas of the amyloid compared to the untreated areas in the contralateral hemisphere. We did this unilateral in a hemisphere so we could use the other side as a control, and we could see a pretty significant reduction in the amyloid in that area.

Now we didn't see a clinical improvement because if you think about the amount of amyloid that's in an individual's brain and we're targeting it in the first person 10cc, you can see it on the images if you look at the publication, but that's not going to make a difference in anybody's clinical outcome, proof of concept, safety, and feasibility, which all seem to happen.

Dr. Wilner:
Hypothetically, you could use focused ultrasound on the entire brain or just maybe the temporoparietal, frontotemporal parietal, or whatever you wanted. Isn't that right?

Dr. Haut:
That is correct. And in the third patient we targeted a little bit in the frontal lobe and a little bit in the temporal lobe, including the hippocampal and entorhinal cortex and some in the parietal cortex also. Again, at that point, 40cc—well, four times as much as the first patient is still not a lot of tissue that you're targeting, but theoretically, we would go after those areas that we thought were safe to target and had a high level of amyloid load based upon their original PET scan, so theoretically, you could do that.

Now to do this procedure safely, they have to be awake while they're in the MRI scan or having this done, and so it takes a pretty long time to get that done for 40cc. So for doing the whole brain, we would have to have approval to make sure that we could sedate them

because it will be much too long a day to be able to hit all that area, and frankly, we don't know if it's safe yet to hit all that tissue at once. You know, we would have to step-wise up. We're thinking about that. That would be important because right now it's a proof of concept. It's not going to have any change in efficacy.

Dr. Wilner:
So what's round two? Where do we go from here?

Dr. Haut:
So round two is right now we're recruiting actively for our next subjects, and they will receive lecanemab, which is the second approved monoclonal antibody. It has full approval. It starts out at the max dose. We can run this trial just as we did before with a single patient to start with a small area, but they will get the max dose, make sure that's safe, and then we can continue to step it up and make sure that it's safe to do that. Again, repeating the feasibility and safety phase of this before we move on to try to tackle efficacy.

Dr. Wilner:
Before we close, Dr. Haut, do you have any takeaway messages for our audience?

Dr. Haut:
I would say currently, the climate for treating Alzheimer's disease is more exciting than it's been in a long time. And I fully acknowledge that the work we're doing is not yet ready for clinical application by a longshot, but the fact that we have these new medicines that have been FDA approved and are disease-modifying to some degree is really exciting for people, not only for patients but also the people who are working in this field, that we actually have a little bit of a toehold. And usually, when you get a toehold, you get a better grasp with the next rounds of everything, so I'm excited to see what happens over the next five to 10 years with other people looking at other medications and other techniques to get a better outcome for people.

Dr. Wilner:
Well, with those final comments in mind, I want to thank my guest, Dr. Marc Haut, for joining me to discuss his research that combined aducanumab and focused ultrasound to open the blood-brain barrier in patients with Alzheimer's disease. Dr. Haut, it was a pleasure having you on the program.

Dr. Haut:
Thank you so much for having me.

Dr. Wilner:
For ReachMD, I'm Dr. Andrew Wilner. To access this and other episodes in our series, visit *NeuroFrontiers* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.