Bob's LAST MARATHON
Living the Alzheimer's Journey

TRANSCRIPT

Progress on Anti-Amyloid Therapies: Roundtable Excerpt 1

Dr. Steven E. Arnold: We are really excited to be in a new era of medical care for people with Alzheimer's disease. And before Dr. Wolk introduces us to the new anti-amyloid therapies for Alzheimer's disease and tells us how the studies went that led to the approval, I'd like to give a little background in history of how we got here, describe what amyloid is and why this is an important target for Alzheimer's disease treatment.

The first thing is that the term *amyloid* itself can be confusing for a lot of people because it's really a general term for misfolded proteins. You know, we have hundreds of thousands of different kinds of protein molecules that make up the different cells and tissues of our body, and many of these protein molecules are dissolved and floating around, either inside or out of the cells, bathing the brain or the heart or the liver.

All protein molecules have a physical structure and for some proteins the structure is more unstable than others, and this makes them vulnerable to folding up and snagging each other and then forming fibrils and clumps of aggregated protein.

So *amyloid* is the general term for these protein fibrils. And these fibrils and the aggregated fibrils that clump up can cause damage to the surrounding tissue.

Now, there are a number of different proteins that can form these amyloid deposits, and different proteins are associated with different diseases. So, for instance, there's a protein called AL amyloid or amyloid light chain that can accumulate in the heart or the kidney and cause heart failure or kidney failure.

In Alzheimer's disease, the protein is called beta amyloid and this accumulates in the brain and forms these plaques and tangles that really define the disease.

Back in the 1890s is when Alois Alzheimer looked through the microscope at the brain tissue of a woman named Auguste Dieter and she had dementia. And when he examined her brain tissue under the microscope after she died, he described the plaques and the tangles that we now use to define Alzheimer's disease.

But it wasn't really until the 1970s or '80s that people really started looking at these plaques and tangles in more detail. Prior to that we called dementia *senile dementia*. And while most of those senile dementias were Alzheimer's disease, we really didn't understand the process at all.

But it was in 1984 that beta amyloid was identified as the specific protein molecule that forms these plaques. A couple of years later, another protein, called tau, that causes the tangles was described. The discovery of those two protein molecules that form these plaques and tangles set off now decades of research into how they were formed, can we actually get rid of them? If we can get rid of them, what happens if we do get rid of them? And it has taken us decades and numerous failures of different treatments and billions and billions of dollars of trials, clinical trials to come to the point that we are now at.

Amyloid molecules are proteins that we have. And they're secreted from cells and they float around and they actually may be helpful for the health of different cells in the brain. But, sometimes these beta amyloid proteins can misfold and crumple up and they form little aggregates called oligomers that can clump up even more and aggregate into what we see under the microscope, which is an amyloid plaque. And these oligomers themselves can be toxic to the brain, and both the oligomers and the plaques can elicit an inflammatory response in the brain that also does damage.

So the new anti-amyloid immunotherapies are really attacking these oligomers and these fibrils. And we have also learned that the anti-amyloid therapies that were tried before and failed actually attacked the single protein molecules. They were not effective and may

have even made people a little bit worse.

So there are the amyloid plaques and then there are the tau tangles. And tau is another protein that instead of being secreted outside of cells is within the cells. And that also can misfold and aggregate into these fibrils that we call neurofibrillary tangles and that can disrupt the activity of the brain cell, ultimately leading to the brain cell dying.

But we're now in a position where we have biomarkers, we have spinal fluid tests, we have PET scans, we even have blood tests now that can measure whether there is amyloid or tau that's developing in the brain. These biomarkers are a total game changer for us, because we can identify with a high degree of certainty that it is amyloid or tau that is causing someone's cognitive difficulty. And we can even detect that very early.

We see some changes in the beta amyloid perhaps 10 or even 20 years before someone has their first symptom and that's followed shortly after by the tau fibrils forming and accumulating in the brain.

And it's only when we start to see some degeneration, when the injury of those amyloid and tau pathologies occurs, that we start to see the memory difficulties. And this really is extraordinarily important because it gives us a window where we can see the disease forming at the earliest stages, and perhaps that is the optimal time for treatment.

Dr. David A. Wolk: I think that was a really nice lead-in for me to briefly go over why it is that lecanemab or Leqembi is the first fully FDA-approved drug for Alzheimer's disease in over 20 years, and the first that is considered "disease modifying" in the sense that it slows down the course of the disease.

As Dr. Arnold showed, there are two main protein aggregates or two main clumps of proteins that occur in the brain with Alzheimer's disease. There are the amyloid plaques and then there are the tau-based neurofibrillary tangles. What Dr. Arnold showed was that the amyloid does seem to be an earlier or an antecedent event in the course of Alzheimer's disease. The tau tangles are actually a bit more tightly linked to the injury to the brain and then to symptoms of the disease.

And so in thinking about treating Alzheimer's disease, one might want to consider removing the plaques, but with the hope that it actually benefits some of these downstream effects on the brain that might also be affecting things such as tau in the brain.

To get specific, the one fully FDA-approved drug is called Leqembi or lecanemab. Lecanemab is an antibody. It's a monoclonal antibody, meaning that it is a single type of antibody that binds to beta amyloid, which is the protein that makes amyloid plaques. But as Dr. Arnold mentioned, it binds to it in the form of oligomers or protofibrils, which are sort of the earlier stages of its clumping together before it forms the plaque itself that we can see under a microscope. And in essence, these are not antibodies that you produce normally. We produce antibodies to all sorts of things. These are antibodies that are given to us through infusion and they bind to amyloid with the idea that they would remove these toxic forms of A-beta. It's also worth noting, though, that they do bind to some extent to the plaques and to some other forms of amyloid as well, but they most strongly bind to the oligomers and protofibrils.

The definitive study for this drug to have been approved was something called CLARITY AD and that was a Phase III, a very large randomized controlled trial.

Phase III trials for medicine are trials that are really looking at whether or not a drug works and those are the trials that go to the FDA for decisions about approval. This trial enrolled around 1800 people who were at very mild stages of Alzheimer's disease. So these were people who were in what we call the mild cognitive impairment stage, which is when people have memory and thinking problems that are more than you expect for age, but they're still able to function pretty well in most of their activities of daily living. It also included people with mild dementia due to Alzheimer's disease. And dementia is when

you're starting to have a little bit more trouble in your capacity to do some of the activities that you would normally do like balance your checkbook or not get lost when driving.

In order to be in the study, and this was actually one of the great advances in general in our field, you had to have a positive amyloid PET scan. So you had to have evidence using those biomarkers that Steven mentioned earlier of the fact that you had the pathology of Alzheimer's disease.

And why that's a big advance is that in many of the trials over the last two decades before we used these biomarkers in our trials, many patients who were included in Alzheimer's trials didn't actually end up having Alzheimer's disease as the underlying diagnosis. So the CLARITY AD trial studied a population we knew had Alzheimer's disease.

And I think one of the really impressive things about this drug is that those that were treated on the drug had really remarkable removal of amyloid plaques from the brain. And the simplest way to think about this is that, by the end of the trial, at 18 months, two-thirds of those people who had a positive amyloid PET scan at the beginning of the trial were considered negative. So a radiologist wouldn't be able to see evidence of amyloid in the brain in 66 percent of those people or around that number. So the drug worked remarkably in removing amyloid from the brain.

For people who've been in this field for a while, taking a step back, it's a remarkable thing that one, we can see that pathology of the disease using these special tests. And two, we could develop a therapy that could actually change the pathology of the disease.

I should also say there was fairly convincing evidence—even though I think there still needs to be more data—that the drug also affected some of the downstream markers of tau pathology in the spinal fluid and blood, and a little bit on some imaging measures of tau. This was observed in a very small number of people, but at least we are starting to see some signal of some of the downstream effects of amyloid on the brain that might suggest that this drug could have a benefit.

None of this would allow the FDA though to approve the drug. These are just sort of supportive features. Really what you want to see is does it have an impact on patients in terms of their thinking and in terms of their function. And indeed there was evidence of this over the 18 months of the study and depending on a variety of different measures that you could look at, there was anywhere from about a 25 to 35 or 40 percent slowing of the disease over time.

For example, those treated with lecanemab showed less change over time compared to the placebo group. And so there's an advantage for the lecanemab group at 18 months, where there was a significantly slower decline in function in the group treated with lecanemab versus placebo. So there was clear evidence of slowing of progression of the disease over this 18-month period and that is the kind of definitive data that led the FDA to approve the drug.

But one way to think about this is, well, how well did this drug reduce the rate of progressing to a clinically meaningful difference over time? So how often does someone go from a milder stage of disease to a more significant stage of disease over the 18 months of the trial? And overall, there was about a 25 percent reduction in that progression. So one in four people didn't go on to a later stage of disease over this period of time compared to the placebo group.

One important thing to keep in mind, and this is one of the challenges of doing these kinds of studies, is Alzheimer's disease is a very slow-moving disease and even in the placebo group about two-thirds of people don't progress over an 18-month time frame.

And so when we talk about the size of the effect of these drugs on outcomes, we have to keep in mind that we're trying to change a slow-moving disease and be able to see signals of change. And so if the disease is not changing a lot just in general over 18 months, the

absolute amount of change that you can observe with a drug is going to be relatively small even though it might have a significant effect on disease slowing.

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