Bob's Last Marathon
Living the Alzheimer's Journey

TRANSCRIPT

The Promise of Anti-Amyloid Therapies: Roundtable Excerpt 2

Dr. David A. Wolk: This is really a major shift in how all of us practice neurology or dementia care for patients with Alzheimer's disease or suspected Alzheimer's disease. It's really complicated administering these drugs; they involve infusions every two weeks for lecanemab. They involve monitoring with MRI scans at various time points to assess for some of the side effects. They involve a fairly detailed evaluation to see if someone's appropriate for lecanemab, and all those steps require coordination across different disciplines and fields and scheduling and insurance and other related issues, so that it really required a health system–wide approach to sort of developing the infrastructure to allow us to start to give patients these drugs.

We went through a process of developing that program that really took us from when the drugs were approved in the middle of the summer to around October or November to have all the pieces in place so that we could administer these drugs as safely and effectively as possible. And we've treated somewhere around a couple dozen people with the drug and we have a relatively long list of people that are kind of on the launching pad to starting with the drug. The other side of challenges in addition to setting things up is actually having the workforce to manage patients with these conditions.

So as everyone here I'm sure is aware, Alzheimer's disease is an extremely common diagnosis and condition, and the number of physicians who really specialize within this area is very, very, very small relative to the population of patients with these conditions that would potentially qualify for lecanemab. And so we've really had struggles, and I've tried to think about ways to increase our capacity as best as possible so that we could move people through this process. And I would say, you know, if there's a bottleneck now that that is the biggest bottleneck for us, being able to see all the patients we would want to evaluate for these drugs relative to the number of clinicians we have to move that process forward.

Dr. Steven E. Arnold: Our experience has been very similar. This is a complicated treatment. We haven't talked yet about some of the safety concerns and possible side effects of the medicines which, while rare, can be serious, and the ethic of "First do no harm." For over a year, we have been getting set up, gathering the clinicians who treat memory disorders in our group, bringing everyone around the table, and coming up with protocols, and coming to consensus about who is the drug right for, who is the drug wrong for, organizing schedules dealing with radiologists so that we can decide on criteria by which we're going to judge MRI scans to see whether it's safe for someone to be on the medicine or to continue on the medicine. There are so many different moving pieces. We formed a specialty clinic for amyloid treatment with about 15 different physicians at our institution, each one of whom takes a week or two weeks of practice for this. We need to train the nurses on the infusion service in some of the particulars of administering the drug. We just opened the clinic about a month and a half or two months ago, and we have a long list of people that are interested. We now have a long list of people who have already been through the clinic and are waiting for the infusions. The process is very slow, and I have to say it's been an appropriately careful rollout.

Felicia Greenfield, MSW, LCSW: Who would you say would be the ideal candidate for Leqembi?

Dr. Wolk: Some of this really reflects the caution that Dr. Arnold referred to. We are very much trying to keep to the way the clinical trials were designed in terms of who we feel is appropriate for the drug. We want people who are in very early stages of Alzheimer's disease, so people who have mild cognitive impairment or very mild dementia, and some of that is based on cutoff scores that we use, and some of that's based on clinician intuition about what degree of impairment someone has. That's one thing just to start with, and actually there is some data that's come out, some of this secondary analysis of the data from this trial as well as with this other drug called donanemab that's very similar—that the more mild range seems to be associated with even better outcomes.

And there is this argument that focusing on amyloid at earlier stages, since it's an earlier event in the disease process, may be when it's most advantageous. In addition to that, there are other factors that may influence your risks of the drug, and those include evidence of what we call amyloid angiopathy. Basically, when amyloid accumulates in the brain, it also can go into blood vessels and cause those blood vessels to be leaky. And it's a pretty common thing we see in Alzheimer's disease just in general, even in untreated patients. One of the side effects of the drug is that when it's given, people can have more leakiness and have what's called edema or some swelling around these blood vessels, or can have even little tiny bleeds from the blood vessels that can be detected on an MRI scan, and very rarely can have a much larger bleed in the brain.

And so what we look for on the MRI scan when we're assessing a patient is do they have evidence already, before we start treatment, of these little tiny bleeds in the brain, which again can occur just with normal Alzheimer's disease. They're very, very tiny. Even though you can see them on an MRI, they're actually much smaller than what we can see with imaging. It seems that the more of those that you have, the higher risk you have of the side effect.

Another feature we look at to stratify both potential benefit and risk is someone's genetic status. So there's a gene called the apolipoprotein E gene, which is the gene that is the largest risk factor for Alzheimer's disease genetically, if you carry a copy of what's called the E4 allele of this gene. So we all have two copies of every gene. We have two copies of apolipoprotein E, and the E4 one is a risk gene for Alzheimer's disease. And having two copies, there's even a higher risk for having Alzheimer's disease. And the reason why that's important here is that also seems to be a risk for the side effect of the little, tiny bleeds I mentioned and the swelling in the brain. And so people who have one or more copies of that gene progressively have more risk.

So the most ideal candidate would be someone who has very, very mild disease, is very, very healthy, doesn't carry this risk gene for Alzheimer's disease and has an MRI without evidence of amyloid angiopathy. If you have one copy of that allele, that increases your risk some for the side effects. And if you have two copies that increases your risk even more. And so those are the kinds of things we discuss with patients in terms of their risk benefit balance.

Dr. Arnold: We only really know the scope of people that have been studied in the research so far. So you know these were people with mild cognitive impairment or very mild stages of dementia. Would it help people who have more advanced disease or more dementia? We just don't know. I think that if we look within the range that Dr. Wolk just talked about, and seeing that people who are at the earlier stages of the disease have the best response and those who are a little bit more advanced may be less likely to respond, I think we can extrapolate to say that it probably won't be that helpful in people that have moderate stages of dementia.

Now, another big question. Indeed, there are several big studies going on now to look at that. What if we could actually treat people before they develop memory problems, but they're already developing that amyloid in the brain? Again, we don't know. We would like to think [we could], we hope that we'll be able to, prevent the emergence of forgetfulness and memory decline if we can see if someone's developing amyloid. But the bottom line is that we really don't know at this point.

And I think that that's something that we're looking forward to in the future as these current research studies unfold. And for all of you either caring for someone with Alzheimer's disease or worried, if you can participate in research so that we can learn these things that'll be a great, great service to the world to have a prevention for Alzheimer's disease.

Beyond that, Dr. Wolk mentioned we can now use PET scans to measure both amyloid and tau. And you could actually see that the people that have the lower levels of tau in the brain when they're treated also seem to have a more beneficial response. This again may suggest that the milder the disease, the more likely you are to going to see an impact.

There are some odd things in the treatment, too, that I don't quite understand yet. If you look at some of the data for lecanemab, men seem to respond a little

bit better than women. I'm not sure why. I'm not even sure whether it was significant or just chance. And then older people tended to respond a little bit better than younger people who had maybe more early-onset Alzheimer's disease, and early-onset Alzheimer's disease tends to be a more aggressive disease. So it may be harder to really fight it and make an impact.

Again, these are questions, these are little interesting points that came up in the study that we don't really understand yet, but I think are worth kind of keeping an eye on.

Ms. Greenfield: We're entering a new era in the treatment of Alzheimer's, which is incredibly exciting and hopeful. What do you think is next, Dr. Arnold?

Dr. Arnold: I like to frame this advance that we have as a huge scientific advance but a modest clinical advance. Dr. Wolk showed that there was clearly a difference between people that were treated with the drug versus those who were not treated with the drug. But still people were getting worse. So overall, on average, people were declining. So why I take real heart in this is that this is the first time after, you know, decades of research that you can actually treat the biology of the disease, treat the pathology, the amyloid, and lower it and actually have it make a difference clinically. And I cannot underscore enough the importance of that, but the clinical effect is modest and we need to do better, we need to do better in a lot of ways. I think we need to make it safer. Serious side effects from this are quite rare, but brain swelling or microbleeds can occur in 20 to 25 percent of people. And you have to stop the treatment if that occurs, at least for a while until it resolves.

With Leqembi, you have to go every two weeks for an infusion. That's a huge burden and a huge expense in terms of time, in terms of transportation, in terms of just the cost of the drug. I think that the company that makes Leqembi is now making a subcutaneous formulation, something that you can inject yourself at home once a week, and that may be available within a year or two. We don't know yet. That is a way that we can get it less burdensome for people and possibly less expensive for people. There will still be the side effects.

And then to the point that you can get rid of amyloid levels in the brain down to indistinguishable from people without Alzheimer's disease, and yet people are still getting worse. That tells me that Alzheimer's disease is more than amyloid and maybe even more than amyloid and tau. And so I think combination therapy is the future. And I think we have to look at the lessons of cancer. Back in the 1940s, childhood leukemia had like a 90 or 95 percent death rate. Sidney Farber started treating people with a drug and he got it down to 85 percent. So 15 percent were surviving.

And then combination therapy—using two to three different approaches to tackle a difficult disease like heart disease, Alzheimer's disease, cancer—came along. This is what we've learned in some of these other fields that have been so successful. And I think that that's what the future also holds. We're going to have to deal with amyloid because it does seem to be, you know, one of the earliest and driving forces of that. But beyond that, we're going to have to do better with tau. We're going to have to do better with inflammation. We're going to have to do better with some of the other metabolic or other things that are part and parcel of the Alzheimer's process. And I'm very optimistic that we're doing that now.

Dr. Wolk: I am pretty optimistic about the future. As Dr. Arnold mentioned, the benefits of this drug on average are pretty modest, but it's a major scientific breakthrough despite that modesty. And I think it also is a major breakthrough in another way in terms of a salubrious side effect if you will, which is that it's forcing us to now really try to characterize our patients as much as possible using the tools that we've used in research for a number of years but that haven't come into clinical practice—which is obtaining PET scans, using spinal fluid studies, potentially blood tests. Now there's an opportunity to measure a variety of different factors incorporating genetics and other types of information. I think you know we have a real opportunity to now move into what in the cancer world is referred to as this precision medicine era where we can really tailor therapies and treatments to an individual patient.

Because if there's one thing I think anyone who's been in this field has learned, it's that patients are

incredibly heterogeneous in terms of the course of the disease, the timing of the disease, the nature of their symptoms, other pathologies that are in the brain, even where Alzheimer's is in the brain in terms of its own pathology itself.

And I think this drug forces us to start to take the kind of information we can use in research and apply it to our clinical populations. And my hope and something we're trying to push here at Penn is that we actually incorporate more research into our clinical practice, so we can see these drugs in the real world.

And what I think will happen in addition to other drugs and other kinds of targets, we'll get better at using the drugs that we have now. I think we'll better learn about people who are going to be more responsive to them versus not. I think there will be an evolution in these drugs in that there are already approaches that might make them safer in terms of the side effects. So at least we're lowering the risk part of the drug. And I think there also will potentially be delivery mechanisms that will help.

And then I think the frontier that Dr. Arnold also alluded to earlier is, if these drugs work in people who are symptomatic, there's pretty good reason to believe that they might work in people before they're symptomatic and delay the time to when people would develop symptoms in the future.

And so I think there's a great deal of hope that this drug opens up. One is just a conceptual hope that yes, we can modify the disease, which I think you know, even though we all kind of believe that, it took 20 years to show that we can do that. But two, I think it just changes the way we practice medicine in this population that will ultimately have downstream effects to really move the field forward.

Dr. Arnold: I like what Dr. Wolk just said, and I wanted to add that precision medicine is what has really made such a difference in cancer. I talked about childhood leukemia having like a 95 percent mortality rate. Well now it has a 95 percent cure rate.

It took decades, but it's there and I think that we can look to a future like that as we understand Alzheimer's better through the research which is now starting to bear real fruit.

Ms. Greenfield: I have a two-part question. If a scan came back positive for amyloid plaque, does it always mean that the patient has tau as well? And the second part of that question is, does an MCI diagnosis with a positive amyloid scan definitely mean an Alzheimer's disease diagnosis?

Dr. Wolk: Those are challenging and really insightful questions. So to the first, there are most certainly people who have amyloid in their brain who, at least based on a tau PET scan, we can't see evidence of downstream tau pathology in those patients. And there's a thought or the argument that those are individuals who are at an earlier stage of disease. There's an argument that amyloid elevates first, and then a number of years down the road, there's a development of tau pathology. And in fact, when we look in cognitively normal older adults, about one-fourth of them have evidence of amyloid in their brain. And if you break down that quarter more, less than half of those people actually also have tau. The thought is that those that don't might develop it at some point in time, although we don't know that for sure.

What we do think is that you don't really start developing symptoms of the disease until you have some of this downstream tau in the brain. And so it is certainly possible that you could have a positive amyloid scan, but it's not Alzheimer's disease that's driving the symptoms that you're having. For example, there are cases that have been reported of people who have a different form of dementia like frontotemporal dementia who have a positive amyloid scan. Pathologically, when those patients have gone on to autopsy, it's really the frontotemporal dementia that was the dominant disease that was driving their symptoms. And so if you have mild cognitive impairment and you have a positive amyloid scan but do not have evidence of tau, it is possible something else is causing your symptoms.

All that being said, at least the way these trials were designed, they wouldn't make that distinction. And there's even some data in those that when you look at the people who had the lowest levels of tau, although it's not really well studied in people who have absent tau but low levels of tau, those people might be the people who respond best to the drug. And so I think

that's one of the nuances and the kind of complexity that we're dealing with with the drug. And I think something we will again learn over time as we treat people with this is, do you have to have some tau or should you have no tau in terms of your likelihood of response.

Ms. Greenfield: Then there's another question about the study that was conducted over 18 months, and how long would you say it takes for the plaques to be completely removed? And how do we know if the drug is having an effect on someone if they continue to show a decline over the course of say maybe 13 to 15 months?

Dr. Arnold: In the studies for Leqembi, it looks like much of the amyloid clearance occurs within the first six to nine months of treatment. So it's actually relatively rapid that you're sucking out the amyloid from the brain, which is really encouraging, and then there's a tail end where you're just cleaning up what's left. But the biggest impact seems to be within the first six to nine months in terms of reducing amyloid, and tau likely follows that. Clinically it's a little more challenging because as we said the measures that we use aren't as good, but there is a general kind of correlation with amyloid removal and improvement, or let's say less decline.

Dr. Wolk: My guess is that the field will move toward us obtaining follow-up amyloid measures to show that the drug is actually affecting the thing that we expect it to affect, which is to lower amyloid in the brain in terms of knowing whether it is having a benefit cognitively. The problem is you don't have the counterfactual, which is what that person would have looked like if they weren't taking the drug. And the big challenge in Alzheimer's is that people decline at very different rates. So it's hard to know in any one individual whether they're declining slower than they would have if they didn't take the drug.

I do think that there is an intuition about that, and there actually are tools that might help us predict what someone who looks a certain way in terms of their amyloid and tau in the brain, how we would expect to see them change, and that those kinds of things might be incorporated into our practice.

And just one other larger point I want to make because we talked about the 18 months and the clearance of amyloid. These drugs, as Dr. Arnold said, tend to clear amyloid. By 18 months in the lecanemab trial, about two-thirds of people had no more amyloid in their brain. We don't know right now if you need to not have amyloid in your brain to slow down the disease or not. And to some extent in an 18-month trial, the faster you lower the amyloid if it is important to get down to a low level, the more time you have to see if the drug has any effect over an 18-month study. And so I do think what is unknown is what happens at 36 months and 48 months and, you know, these other times down the road.

And I think if the drug continues to have a modifying effect over that time, I think it'll be easier to see differences from expectation over longer periods of time than over these sort of short periods where the amount of change is relatively small even in people not treated with the drug.

Ms. Greenfield: Has there been any noticeable increase in side effects the longer a patient's been on the drug? If not, is there concern for this if the patient's taking the drug for five-plus years instead of the two involved in the FDA approval study?

Dr. Wolk: In general if anything it's the opposite of that. When people have side effects, it tends to be early in the course of disease, at least the ones that we were talking about—the swelling or the microhemorrhages. And so those tend to occur within the first three to six months of treatment when there's a high load of amyloid in their brain. As people continue in treatment, those numbers go down pretty significantly. And that's why the monitoring with MRI scans is much more spread out and not necessarily even required over longer periods of time.

There are a number of people who've been into open label phases of these drugs followed two, three, four years, and as far as I know it doesn't seem like there's an increase in side effects as a result. We obviously have not treated people for years and years and years with these drugs to know for sure, and the population of people who have been treated for three, four, five years is lower. But if anything, the intuition is that the major side effects, which again are the swelling

and these microhemorrhages, as well as transfusion reactions, all tend to be things that are early in the treatment phase and not later in the treatment phase.

Ms. Greenfield: Are there genetic backgrounds that correlate with the response?

Dr. Wolk: The simplistic answer is that in general there's higher amyloid load in E4 carriers than non-carriers and more of this amyloid angiopathy where there are amyloids in the blood vessels. And that combination seems to result in people having more of this side effect. In general, in Alzheimer's, even though APOE E4 is a risk factor, about half of people with Alzheimer's don't have that gene. So it's really just a risk factor, but it happens to be a risk factor that interacts with the risk of this drug, the risk factor for Alzheimer's that interacts with the risk of the drug.

Ms. Greenfield: What if somebody has one copy of APOE E4 and one copy of APOE E2? Is that a good combination for treatment or not?

Dr. Arnold: The APOE E2 is relatively rare, but you know we consider the treatment safe for people with one copy of the APOE E4 gene. One copy of the E4 gene increases your risk. Two copies of the E4 gene, as Dr. Wolk said, increases your risk considerably more. E2 is actually a little bit protective and it decreases the risk. So I don't know what the data is, but if anything I would think it might decrease your risk for the side effects a little bit, but I really don't know.

One thing I guess just to bring up with the E4 and risk, and risk in general, and that I have found at least in my experience in dealing with patients, is that for a lot of this the best we can do is to say what are the risks that are out there that we know of. People's risk tolerance really varies.

The way that often these side effects are described, you know, it's still percentage-wise a relatively small percent of people, on the order of a few percent, that have a more significant severe, if non-reversible, effect. Because usually even when people are symptomatic with these side effects, they're reversible. It's actually only in about 1 to 2 percent, 1 percent in lecanemab, 2 percent in donanemab, where it's not some more sustained very serious side effect, but people vary.

Some people say, you know I want to do anything I can to stay where I am now and for as long as we can, and I accept you know a 5 percent risk of a more serious outcome, a 10 percent risk of a more serious outcome. And so a lot of this I do think ultimately comes down to conversations between patients and their physician and their families in terms of what's acceptable to them. And we can provide guidance in terms of what we know from the data. But these are kind of personal, I think, decisions.

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