Positive Results in Alzheimer's: Are We Now Pushing the Right Buttons?

PODCAST 29

00:45
Dr. Jane Caldwell
Today *On Medical Grounds*, we will be speaking with Dr. Curtis Schreiber. Dr. Schreiber is medical director at the Missouri Memory Center and the CMH Neurology and Headache Center, all headquartered at Citizens Memorial Health Care in Bolivar, Missouri. Patients at the Missouri Memory Center at Citizens Memorial Hospital recently participated in an international clinical trial for treatment of Alzheimer's disease.

Donanemab significantly slowed cognitive and functional decline in patients with early symptomatic Alzheimer's disease. Dr. Schreiber was the principal investigator at Missouri Memory Center on the study, which started in 2021 and just presented top line results in May of 2023. Hello, Dr. Schreiber. Welcome to *On Medical Grounds*.

Dr. Curtis Schreiber
Well, thank you and thank you for having me.

01:43
Dr. Jane Caldwell
In a statement on the Missouri Memory Center website, you said the following, "Results of studies such as these offer hope to patients, families, and medical care providers that wrestle with the devastation of Alzheimer's disease. Options for slowing this unforgiving disease may be on the horizon". What has triggered your optimism?

Dr. Curtis Schreiber
Well, Jane, I've been practicing in neurology and taking care of Alzheimer's patients for over 30 years. You know, we have been waiting and watching and hoping that we might find more effective ways to help patients and their families with Alzheimer's disease. 2023 is going to be a banner year, a banner year for Alzheimer's disease treatment, Alzheimer's disease patients, because we're going to see the announcements very shortly of new treatments being available for Alzheimer's disease. We've not had that. We're talking about not just treating symptoms. We've had some symptom treatments for quite some time, but we've been waiting and hoping for treatments that may change the disease process, to slow the disease process. And I'm optimistic that we're seeing, for the first time, clinical trial results that are pointing in that direction for us and for our patients very soon.

03:03
Dr. Jane Caldwell
That's super. What are the statistical findings of this phase III trial?

Dr. Curtis Schreiber
So the top line results of the phase III study for donanemab have just been released. Now top line, what that means is the very first pieces of information and really the very top pieces. When you look at a clinical trial, the number one thing we look at is what's called the primary outcome measure. That's what has to be positive for the study to be a positive study. And then secondary outcome measures, they're important scientific pieces, but they're also being presented.

So the top line result for the donanemab phase III clinical trial that was just announced in May, is for the outcome measure that measures a combination of cognition, meaning memory and thinking skills, plus function, meaning what's going on at home. How does the person function in their everyday life? And that primary outcome measure is pivotal for a drug to be considered for possible FDA approval.

In the phase III study for donanemab that was recently announced, the primary outcome measure is something called the iARDS [Integrated Alzheimer's Disease Rating Scale]. That's just an acronym for this measurement. And in the phase III study for donanemab, what was shown was that over the 18 months of the study, there was a 35% relative slowing in that outcome measure. That outcome measure meaning combined cognitive scales and functional scales; what's going on with memory and thinking as far as testing, and what's going on with how things are at home. And so this is news. This is news that we have treatments now that have clinical trial data to show a slowing of the progress of Alzheimer's.

04:53
Dr. Jane Caldwell
You know, Bolivar, Missouri is not a large metropolis. How did you attract this big study?

Dr. Curtis Schreiber
So, Jane, I've been working in the field of Alzheimer's disease for a whole 30 years. And in 1999, I had the great opportunity to start a memory center. In 2016, in Bolivar, we started the Missouri Memory Center program. And really this came to us because we've been in the trenches, we've been working with patients. I've had some clinical trial experience in the past and in the present as well. And due to the fact that we're taking care of patients, we were invited to participate in this large, really international study. So, Jane, this study had over 1,700 patients around the world in the study. And you're right, Bolivar, Missouri is not the center of the universe, nor the center of Missouri, but we were a clinical site in this trial and we contributed 13 subjects to this large study.

05:50
Dr. Jane Caldwell
Well, that answers my next question, how many participants were in this trial, but how were they selected and how were they recruited?

Dr. Curtis Schreiber
So that's a really important question because the type of patients that were in the study are going to be the type of patients that would be candidates in the future for these medications when they become available. Alzheimer's disease is a gradually progressing disorder. And it's easy for most people to identify a person that's well-progressed, that's fairly far down the road with Alzheimer's disease.

Yet we don't think that these treatments are likely to be effective for people that have progressed to moderate or severe stages. And in fact, moderate to severe patients were not part of the clinical trial and they will probably not be candidates for this type of treatment when it does become available. The kind of patients that were enrolled into the study are those that have either diagnosed Alzheimer's disease in the mild stage or what's called mild cognitive impairment with Alzheimer's disease being the process underneath it. So really when we think about who was enrolled, we need to know that these were patients that were showing up early in the course of Alzheimer's.

07:07
Dr. Jane Caldwell
So what is donanemab and how is it produced?

Dr. Curtis Schreiber
So, donanemab is a monoclonal antibody treatment for Alzheimer's disease. Forever, we've known that amyloid, a protein, a normal protein that accumulates abnormally in the brain of Alzheimer's patients is part of Alzheimer's disease. In fact, if you take it back to the very beginning, it was Dr. Alzheimer who first discovered amyloid and tau, the two pivotal proteins that are in the brain and are required for the diagnosis of Alzheimer's disease.

Donanemab is an antibody that was specifically custom designed to remove that accumulation of amyloid called an amyloid plaque that builds up in the brain of patients with Alzheimer's disease. And so it's a targeted therapy. It's targeted to remove the amyloid plaque from the brain of patients who have early Alzheimer's disease.

08:05
Dr. Jane Caldwell
Why do you think it works?

Dr. Curtis Schreiber
So the reason that this treatment can be effective is because amyloid is part of the process. Now amyloid has been a target for treatment for many years, for decades, and there have been various types of approaches to removing amyloid from the brain. What we have currently are targeted treatments to get it at the plaque stage. So the theory, the theory is that by removing the amyloid plaque from the brain, that it reduces the other changes that develop as the disease progresses. So the exact mechanism, the mechanism we know is to remove amyloid plaque from the brain. How that changes the course of Alzheimer's disease is really based on the theory that the amyloid plaque development leads to a cascade of other changes that cause the progression of Alzheimer's disease.

09:04
Dr. Jane Caldwell
How is donanemab administered?

Dr. Curtis Schreiber
Donanemab is administered as an intravenous infusion. It's administered intravenously once a month, every four weeks.

09:19
Dr. Jane Caldwell
What about side effects?

Dr. Curtis Schreiber
So this is always important. We always want to make sure we're looking at the possible benefits, but we need to evaluate the possible risks. So improvement versus potential side effects. As we've stated earlier, there are indications that the drug will reduce the progression of the cognitive and functional decline by 35% at the 18-month time point. But we need to look at possible side effects. In this class of medications, meaning medicines that are monoclonal antibodies that remove amyloid from the brain, there are the concerns for a change in the brain called ARIA. Those are four letters, A-R-I-A, which stand for amyloid-related imaging abnormalities. So what that means in real terms is, we can see things that change in the brain with the administration of this type of medication. And we find it because we know we're going to be checking for it. In clinical trials, we're always looking at safety of patients number one. Safety is number one. And in the clinical trials for donanemab and for others in this class, during the trials there are periodic scheduled MRI scans to monitor for these changes in the brain called ARIA.

So ARIA can have two forms. One is called ARIA-E and the other is called ARIA-H. ARIA-E means edema. Edema means that there's areas in the brain where there's indications that they're swelling. Now, ARIA-H, H stands for hemorrhage. H means that there can be areas in the brain that show that there's been leakage of blood from blood vessels. Now, we definitely are concerned about those. You know, most of the patients that have ARIA, it's not symptomatic, there's no symptoms, but that's not all of the patients. For example, in this study that we're discussing, the phase III study for donanemab for Alzheimer's disease, the ARIA-E rate in the treatment group was about 24%. About one in four people in the clinical trial did show changes of ARIA-E. Now, most of those have no symptoms. Of those that have ARIA-E, only about 6% of the patients that had this occurrence had symptoms. Most are found asymptomatically on routine scanning. Most do not have symptoms. But there can be patients with serious symptoms.

Now, ARIA-H, that's the other type of ARIA, in the donanemab phase III clinical trial, 31% of people had ARIA-H found on MRI scanning. Now, there were also some people that had similar findings in the placebo group. There's a big explanation behind why that would be likely to happen, but those were the occurrence of ARIA. Now, as I stated, most patients are asymptomatic with ARIA, but unfortunately, some can have serious complications of ARIA. In the donanemab clinical trial for the phase III study, 1.6% of patients had serious ARIA. So 1.6% of patients on treatment had serious ARIA findings, including in this study, there are two participants whose deaths were attributed to ARIA. One participant expired after an incident of serious ARIA. Whether that was connected, they are still determining, but we do know that there are these potential risks. Another possible side effect of this medicine, and really, well, any medicine that's given as an intravenous infusion, is the chance of having what are called infusion-related reactions. Those are things that can occur due to the fact that a monoclonal antibody is being infused into the system. And in the phase III clinical trial for donanemab, 8.7% of people did experience an infusion related reaction. Now most cases were mild to moderate, but those are really the biggest concerns. Those are things that as clinicians, we need to be able to describe to patients and families so that they can make their judgment about should they proceed with this type of treatment. The benefits, the risks, and how does that work out for them for what they want to do with their treatment.

So I think it's important to look at the good news, and there is good news here, but it's important to look at the other news, and we need to be attentive to this and be able to explain to our patients and their families the benefits and the risks of this type of treatment.

13:58
Dr. Jane Caldwell
I see. So how does donanemab compare to drugs already on the market?

Dr. Curtis Schreiber
Interesting question, in this world of monoclonal antibodies for Alzheimer's disease, there have been two approvals up to this point for this class of medicines. Both of those are considered to be accelerated approvals. Accelerated means they were approved based on their findings for amyloid removal, but they've not yet received full approval for Alzheimer's disease treatment from the FDA.

So I expect we're going to be seeing some exciting news. I think we will see one of those other two achieve FDA approval. It seems to be likely that will be occurring here this summer. Donanemab is going through that process of FDA approval now. And so we'll need to wait. I think we're going to see later this year whether the FDA will signal full approval for donanemab based on this phase III study. These results are strong and we will be waiting to see what the final authorities decide regarding full FDA approval.

15:14
Dr. Jane Caldwell
So let's go back to the study itself. How do you normalize the study participants? Doesn't personal lifestyle have an effect on dementia progression?

Dr. Curtis Schreiber
Jane, that's a really great question. Certainly we think that there are ways that people can help themselves. There are ways that people can help protect their brain. There are ways that we all should be taking care of our body and our brain from the very beginning, not just when we develop the symptoms of a disease like Alzheimer's disease. So in general, when you look at the inclusion criteria, I mean, it certainly doesn't individually stratify it based on lifestyle issues. It's really based primarily on overall health. So one might say, yes, these are probably a healthier group than people that don't mind their health because certainly severe chronic diseases would be exclusionary from the clinical trial entry. However, with regards to stratifying based on things that we hope are important, like exercise and diet and maintaining cognitive health by using our brain with hobbies and activities, those specific things were not stratified in this clinical trial. And they haven't been in any trial.

16:30
Dr. Jane Caldwell
Is there any data to support lifestyle modifications which may help prevent or slow the progression of Alzheimer's?

Dr. Curtis Schreiber
That also is a great topic of discussion. And the answer is that the data is coming. It's hard to measure these things because a lot of these are self-reported, meaning what was your diet like? Did you follow your diet?

You told us that you're going to exercise. Did you really exercise? You told us that you were participating in community activities to maintain your cognitive health by social interaction. Are you really doing it? So yes, there are studies that are coming along. And I think we're starting to see that the common sense suggestion. Common sense would say do good things for your brain and your brain will be healthier. I think we're starting to see that those things are actually proven scientifically. One thing that's really come along in this field is it turns out, believe it or not, that the obvious thing that what's good for your heart is also good for your brain. We've known this in cardiac disease for a long time, right? Follow a good diet, use the Mediterranean diet. You have to exercise, you'll stay fit. All those things are important for the heart and I think we're going to be seeing that all those things are similarly important for the brain.

17:49

Dr. Jane Caldwell

Could you discuss the genetic component of Alzheimer's?

Dr. Curtis Schreiber

So that's a really interesting topic. There are genetic influences on Alzheimer's disease and they range from really serious genetics like autosomal dominant cases. There are some cases of people that do have what's called an autosomal dominant inheritance. That means there's specific genes that are passed through in the family that people will develop Alzheimer's disease. The thing about that type of genetic transmission of Alzheimer's disease is that almost always those cases show up at unusually young ages. I'm talking people that get Alzheimer's disease in their 50s or 40s or 30s. There are some cases like that. Those are highly rare and we don't really test for that kind of genetic transmission unless there's a story that goes along with it that would point towards that. Most people that develop Alzheimer's disease, including those that start at somewhat younger ages, like in their 60s, they do not have that specific autosomal dominance.

Now, the one thing that we do know that is a risk factor for Alzheimer's disease, but doesn't really cause it directly, is apolipoprotein E. So there are some genetic tests that use the ApoE or apolipoprotein E testing to see if there's a risk factor for Alzheimer's disease, but that testing doesn't clearly indicate that everyone that has that certain combination will always get Alzheimer's disease. And Jane, there are many other genes. There are many other genes that we know about and probably even more we're going to discover, hopefully, in the future to determine the genetic link for Alzheimer's disease. Not everyone that has a first order family member, meaning a parent or a sibling, not everyone that has a parent or a sibling with Alzheimer's disease is destined to have Alzheimer's disease, but it does increase the risk. And you know, in my practice, I think it's really important to counsel people that are there with their loved ones. That even though they're worried, they're anxious because they're sitting with their mom or their dad or their brother or sister who's having a diagnosis that day of Alzheimer's disease, everybody that is in that situation has a chance, I think, to help themselves. And the best chance is to do those things that we just talked about, to take care of their health, to take care of their diet, their exercise, their social interaction. Those can all influence whether or not a person will develop Alzheimer's disease. And we hope that by following good health habits, if they do have genetic predisposition, it would prevent or delay Alzheimer's disease as well. I think it's great that we're entering an era that we can offer treatments to people that will have Alzheimer's disease at early stages with the hope of slowing the progression. But the biggest hope for people is really to do the more obvious thing, try to take care of your health, your brain, your body. And I think those things are probably going to be one of our biggest interventions to try to help people prevent progressing into diagnosable Alzheimer's.

21:05

Dr. Jane Caldwell

Dr. Schreiber, you began your career as an electrical engineer working in NASA's Project Galileo mission to Jupiter. Why did you change to neurology?

Dr. Curtis Schreiber

Jane, you know, it's all about circuits, right? Certainly as I was going through my early years of education and actually employment too, I was drawn towards figuring things out. And figuring things out with electronics that was just up my alley. You might say it was a no brainer at that point. As I progressed in my interest, I found out that there's this thing called the brain that actually is a big complicated challenging electrical phenomenon that turns flesh into person, that makes us who we are. And when I learned more about that, I thought there's another area. It's really going from hardware, like designing electronic circuits for a spacecraft, to what we somewhat jokingly call wetware. Wetware meaning the brain inside of our head. And so for me, it was a real natural transition. And it gave me the opportunity to kind of follow what I think is a core interest for me, which is to find problems and look for solutions and troubleshoot things. Plus, the great thing is, when you're working with people, you change lives.

22:30

Dr. Jane Caldwell

Do you have a personal reason for studying Alzheimer's?

Dr. Curtis Schreiber

My personal reason for studying Alzheimer's is what happened to me when I entered my clinical practice. And that was in 1991 when I finished my residency. And in those days we would sit down with people and we could see people coming in that we knew had Alzheimer's disease. We didn't have all the tools, clinical tools or laboratory tools that we have now to help with the diagnosis, but we would know in our heart of hearts that this was what that person was dealing with. And it was challenging, it was tough.

It was tough to be counseling people to say, I think we've got a big problem here, but not having much of a big solution. So, for me, the hope was twofold. One, to help guide people or help people through their most challenging walk of their life with Alzheimer's disease, but also to work on the solutions, to see are there things that can be done? Can we be part of the solution? And that's why our participation at Missouri Memory Center in this phase III clinical trial that did come up with a positive result has been so rewarding. It's been a great enjoyment for me to be able to participate and be part of what we hope will be a solution now and hopefully a bigger solution as we learn more about the science of Alzheimer's.

23:54

Dr. Jane Caldwell

You've mentioned hope in several sentences just now. How do you provide hope for Alzheimer's patients and their caregivers?

Dr. Curtis Schreiber

What we do is we sit down with people and when we deliver this devastating message to them, they feel like there's no hope. They feel like there's nothing they can do. They feel like they're powerless. And even

now, even now when we don't have the treatments that can at this point slow the progression, we hope to have those soon. You know, there are ways that we can help people.

There is hope, there is help, and the important things is for people to recognize there is a problem, to know what to expect, to be able to make the best of the situation, the best of the caregiving, the best of their lives, so that they are in their own power. They have the power of knowledge to make the best decisions to take care of themselves and their families.

24:51
Dr. Jane Caldwell
Dr. Schreiber, we applaud your team's research efforts to slow the progression of early Alzheimer's disease. Thank you so much for taking time from your busy schedule to speak with us.

Dr. Curtis Schreiber
Well, thank you and really thank you for bringing this topic to your podcast and getting the word out.

Dr. Jane Caldwell
And thank you for listening to the *On Medical Grounds* podcast. We know your time is valuable.

The resources that we've referred to in this podcast can be found at **OnMedicalGrounds.com**. Be sure to click the subscribe button to be alerted when we post new content. If you enjoyed this podcast, please rate and review it and share it with your friends and colleagues.

MISSOURI MEMORY CENTER STUDY SUMMARY:

In the phase III study, donanemab significantly slowed cognitive and functional decline in patients with early symptomatic Alzheimer's. Results reported by Eli Lilly & Co. include:

- 47% of participants on donanemab showed no decline based on a key measure of disease severity at one year compared to 29% of participants on placebo.
- Participants on donanemab had a 40% less decline in their ability to perform activities of daily living at 18 months.
- Participants on donanemab experienced a 39% lower risk of progressing to the next stage of disease compared to placebo.