

Mayo Clinic Q & A - Dr. Petersen and Dr. Knopman - YouTube A...

Mon, 6/14 7:17PM 18:44

SUMMARY KEYWORDS

patients, drug, alzheimer, disease, clinical, question, benefits, mayo clinic, amyloid, people, fda, amyloid plaques, therapies, cholinesterase inhibitors, jake, called, petersen, treat, ultimately, field

SPEAKERS

Narrator, Ronald Petersen, M.D., Jacob Strand, M.D., David S. Knopman, M.D.

- N** Narrator 00:00
Coming up on Mayo Clinic Q&A,
- D** David S. Knopman, M.D. 00:02
But it's trying to maintain function and daily life and maintain as much independence as possible. Alzheimer's disease is a devastating illness that can impact the lives of those diagnosed and their loved ones. Recently, the FDA granted approval of a new Alzheimer's drug to fight this illness. Our experts weigh in on the effectiveness of the new drug.
- R** Ronald Petersen, M.D. 00:25
I believe that part of the FDA's response here was that this is a fatal disease. People will progress, they will die from this disorder, and we do not have anything else right now to offer them.
- J** Jacob Strand, M.D. 00:40
Welcome everyone to Mayo Clinic Q&A. I'm Dr. Jake strand sitting in for Dr. Halena Gazelka. Earlier this week, the Food and Drug Administration approved Aducanumab to

treat Alzheimer's disease. Aducanumab, targets amyloid plaques in the brain that are believed to be an essential component of Alzheimer's disease. But 6 million people in the United States and 30 million people worldwide are currently living with Alzheimer's disease, a progressive brain disorder that is the most common cause of dementia. What does this news mean for Alzheimer's patients? Here to discuss is Mayo Clinic neurologist and director of Mayo Clinic's Alzheimer's Disease Research Center, Dr. Ronald Peterson, and Mayo Clinic neurologist, Dr. David Knopman. Well, let's start with you Dr. Peterson. Can you just tell us a little bit about what this drug is designed to do to help patients with Alzheimer's disease?

R

Ronald Petersen, M.D. 01:29

Sure, Jake. So, Aducanumab is a monoclonal antibody that is designed to be infused into the bloodstream, get into the brain, and remove amyloid plaques from the brain. Two of the defining features of Alzheimer's disease are the presence of amyloid plaques, and tau base tangles. This drug is designed to get the amyloid plaque out of the brain or at least reduce the amount of amyloid in the brain.

J

Jacob Strand, M.D. 01:57

That's really helpful. I imagine a lot of patients when they first heard the news that there was a new treatment for Alzheimer's may have been envisioning a pill or some other pills that are used for Alzheimer's symptoms that some may be aware of. You mentioned this as an infusion. What does it look like for a patient as they might be available for a treatment regimen? What does that mean for their treatment course?

R

Ronald Petersen, M.D. 02:19

So, if a patient were to receive this drug, he or she would come into a medical facility, have an intravenous line put in the arm, and then sit there in the chair while the drug is infused for about an hour, and then watched for a little while and then dismissed. So, it does require an infusion, usually at a medical center. Occasionally, there are these home infusion services. So, conceivably, it could be done at home. But generally, it's done in a medical center to monitor it for safety.

J

Jacob Strand, M.D. 02:52

That's really helpful, and I think maybe just turning a little bit to some of the news recently, because I imagine there's a lot of questions, and I know you all have been fielding lots of questions. You know, this was subject to a pretty intense debate. I work with a lot of

patients who have already asked some of my colleague's questions. I have family members who have Alzheimer's disease, and they're calling with questions. And so maybe Dr. Knopman, I could ask you, can you talk to us a little bit about some of the debate around this? I know it's hard to put into words, but maybe we can talk about it and how you will talk to your patients about the risks and benefits.

D

David S. Knopman, M.D. 03:24

Right. Thanks, Jake. Well, it's been a very contentious discussion that's been going on for two years. And it would take hours to describe all of that. But briefly, the studies on which this approval was based were terminated prematurely, or terminated back in March of 2019, when the company initially concluded that the drug did not show benefits, they then changed their mind. They presented it to an FDA advisory committee with the approval of the FDA leadership in November of 2020. The Advisory Committee roundly rejected the idea that it had clinical benefits, to be very blunt. And then the FDA leadership took this under advisement. And then with their report on Monday, they approved it in what's called an accelerated approval, in which they based the approval on the fact that it lowered brain amyloid, even though the clinical benefits were, let's say, uncertain. And that then is that segue to what I would say to patients. Even though my opinion might be clear from what I just said, I will offer it to patients and will discuss it with them if the patient and family brings it up. But I will present both sides. What its possibilities might be for slowing decline of disease, never bringing about improvement, by the way, and the possibility that it may have minimal benefits and let them decide.

J

Jacob Strand, M.D. 05:08

Well, I think that's really a helpful piece as we think about, you know, maybe this next step, which sounds like there's even going to be because of all this disagreement, another clinical trial, and maybe Dr. Petersen, can you tell us a little bit about this additional clinical trial, since it wasn't approved based on efficacy, they're gonna do another trial about efficacy. What is that going to mean for patients?

R

Ronald Petersen, M.D. 05:31

Well, it's an interesting situation, because the drug will be available clinically, so physicians can prescribe it and patients can receive it. But as Dr. Knopman indicated, the FDA was uncertain as to the clinical utility of the drugs. So, they're requiring the sponsor, to do a phase 4 study, another study using the drug and seeing if it produces a clinical benefit. And if it does not, the FDA will remove the drug from the market. But during the interim, the drug will be available to patients. So, it'll be incumbent upon the clinicians

then to really describe the pluses and minuses of this situation. And hopefully, the patients and families will make an informed decision as to whether they want to undertake the treatment with the drug or not.

J

Jacob Strand, M.D. 06:21

Yeah. And maybe we can put within that, that kind of back and forth and these pros and cons. I know, there's been certainly as a person, not an expert in the field of Alzheimer's disease, but again, taking care of a lot of patients where that's really a key facet in our life. There's a great deal of fear about this diagnosis, and certainly a significant societal impact. And there's also been, you know, hopes before of other drugs and even sounds like other drugs that have impacted these amyloid plaques. Dr. Knopman, what does this mean for kind of the history of these drugs? And can you talk a little bit about this idea that amyloid plaques, we haven't shown there to be benefit yet? And so, what does that mean for patients who are hoping for something that may help even if it's uncertain?

D

David S. Knopman, M.D. 07:10

Well Jake, that's a really good question. And I think that this FDA approval, has made the situation actually even more complex, because it raises the possibility of what I think psychiatrists call therapeutic misunderstandings. In the lay press, one might have the sense that this drug brought about improvement. And there's no question that it never improved patients. At the best, it delayed progression. And we have experience with that in our field. It's with the existing very modest cholinesterase inhibitor drugs, that it's very difficult to see, delay, and justify or understand, or appreciate delay in progression. And the other issue, which we don't have hours to talk about, is whether the lowering of amyloid realistically has any prospect of eventually bringing about clinical benefit. We recall that these studies were 18 months in duration, and they didn't see clinical benefit. Yet the FDA approval was on the expectation that at some point in the future, it would. But to me, that seems like a real promise that is going to be difficult to fulfill.

J

Jacob Strand, M.D. 08:42

And maybe that's a really important question I could ask Dr. Petersen as a follow-up, you know, this idea of these short duration, we know that patients live for many, many years with Alzheimer's disease. You mentioned a little bit about this additional clinical trial that will take place, and the fact that that will be a challenge because there'll be people also able to instead of you know getting the drug or maybe a placebo, they can go to somewhere where they can get the drug prescribed potentially. What sort of surveillance is the FDA and the companies and the healthcare systems going to do to see if 36 months

you know, five years down the line, if this has shown benefit? Do we have any information about that yet?

R

Ronald Petersen, M.D. 09:24

Yeah, it's an interesting situation Jake as to how the FDA will make the decision ultimately. They base it on the the outcome of the phase 4 trial, but clearly, there'll be a lot of data generated by the clinical community over the timeframe. And I think it's incumbent upon medical systems, Mayo being one of them, to generate reliable and valid data. So, I think we are going to develop a program that is designed to determine which patients might be most eligible for the treatment, and then we will follow them very closely clinically to determine what, if anything, is happening with the drug clearly from a safety perspective, but also from an efficacy point of view, that is the drug stabilizing their clinical condition. Now, keeping in mind, we'll just have to use historical controls, like how would people have progressed over this timeframe if they were not treated with the drug. So, that will be a challenge. The company is also establishing registries around the country to follow patients in a more organized fashion, whether that's going to produce useful data, I think, remains to be seen.

J

Jacob Strand, M.D. 10:39

I think the hope, of course, for a lot of patients, I heard an interview with members of the public and members of societies advocating for patients and their caregivers with Alzheimer disease, that, you know, we don't really feel like we have anything and so something is better than nothing. And we can argue about that and the cost of that, both to the patient in terms of time and also from a cost perspective of the drug itself. But what I hear in those comments is this hope that this is just the beginning, that maybe this will help spur other types of therapies. And I wonder if you could share, Dr. Peterson, I'll ask both of you this question. What else is on the horizon? And kind of taking from this the lesson of this kind of very complicated issue?

R

Ronald Petersen, M.D. 11:22

Yeah, I might just comment Jake, on your earlier observation that this may be just the first step in this direction. You know, Dr. Knopman mentioned that decades ago, he and I were around when cholinesterase inhibitors were introduced to the market. The first drug out there was something called Tacrine, which had a relatively short shelf life on the clinical field, because it was really not very good. But it did open the door for other cholinesterase inhibitors. Granted, they're just symptomatic medications, but three others followed, have been FDA approved, and now we've been used for many, many years to try to stabilize

some of the symptoms. I kind of view this in the same perspective. That is, this is the first of the disease modifying therapies. I think there will be others coming down the road, and probably better, and then it'll remain the question of are these disease modifying therapies actually effective at what they're doing? So, I mean, I think it's going to be an interesting story to follow. We're getting more sophisticated with regard to our evaluation of appropriate patients for these studies. I think our measurement techniques are getting better looking at the biomarkers that categorize people. So, you know, I'm optimistic that we're going to learn a lot more. And I believe that part of the FDA's response here was that this is a fatal disease, people will progress, they will die from this disorder, and we do not have anything else right now to offer them. And so, I think that that entered into their decision as well.

J

Jacob Strand, M.D. 13:03

Yeah. And thanks for reflecting on that, and I think this piece about these other therapies, Doctor Knopman, maybe the same question for you. What do you see on the horizon?

D

David S. Knopman, M.D. 13:15

I'm more impressed by how the need will generate new ideas. And putting out a therapy that may have minimal benefits, I don't think will particularly accomplish that goal. I think the key is to find better targets for therapy 50 or 60 years where cancer chemotherapy was in the doldrums with relatively few benefits. And then along came the checkpoint inhibitors and other agents that were specific for particular mutations in solid tumors, and boom, all of a sudden, you're seeing real benefits. And I'm not sure that the decades of treating with the traditional antineoplastic agents really enabled that process as much as the continued need of the failure of those agents ultimately, to bring about real benefit. And that's how I see the situation here. It's the need to have better therapies. And I do think that in my capacity in reviewing grants of phase 1 and phase 2 studies in this field, that there's tremendous ferment underneath in the biology of the disease and finding better targets. And so, I'm hopeful in the future, that we'll get lucky and find one that's much more potent than Aducanumab.

R

Ronald Petersen, M.D. 14:49

You know, Jake, if I may comment on Dave's observation. I think he's quite right, though this might be the first step such that ultimately, I think we're going to use combination therapy to treat cognitive disorders and aging. So, it may be that while amyloid modulation may not provide a significant clinical impact, with it being on board, we might add, say, an anti-tau or an anti-tangle agent. And that combination may very well be

effective. Whether you need the amyloid backbone on which to treat the tau, so I think it opens the door for a variety of other combinatorial therapies that might be developed in the future.

J

Jacob Strand, M.D. 15:34

Well, maybe kind of a last question, you know, one of the things that I think both of you have hit on, which is so critical is this idea that we're all still struggling to figure out what the best outcomes to look at are, and how we take care of patients ultimately, And I think I'm certainly believed by the idea that Mayo Clinic continues to lead in figuring out the right biomarkers and the right way to follow patients so that we can really target these cures to the right patients. And something else that I just wanted to ask about is how, maybe if this made an impact on a specific score, or, you know, cognitive decline, it didn't show, what does it mean for quality of life? And is that something that will, as an outcome measure? What is the difference it's making in people's functional status and their quality of life over time? Do we have a sense of where the state of research is in following a drug like Aducanumab for those types of endpoints?

D

David S. Knopman, M.D. 16:30

Which I'll go first here, I think that's really a key question. And we don't really know the answer exactly. Personally, I think that it's how people do in day-to-day affairs, that counts. I don't really care as much about a mental status exam, except if it confirms what we're hearing from the family. But ultimately, we'd like stabilization of function at a high level of near independence. We don't know what we would ultimately settle for if that's the best we could do. But it's trying to maintain function in daily life and maintain as much independence as possible. That ultimately is the key, and we don't really know how much of that is enough.

R

Ronald Petersen, M.D. 17:20

Yeah, yeah, it really it really comes down to what's called clinical meaningfulness. So how do you measure that? How do you measure how a person is functioning? Actually, here at Mayo, Dave and I are involved in a study called the Mayo Clinic Study of Aging, where we're following people who live in the community here in Rochester and Olmsted County. And this is a random sample of people as they're aging in place. And we are capturing a good deal of cognitive and functional data on them. And I think we're in a pretty good place to offer some reflections on what constitutes a clinical meaningful scale, and we're trying to contribute to the field in that respect.



Jacob Strand, M.D. 18:02

Our thanks to Mayo Clinic neurologist Dr. Ronald Petersen, and Dr. David Knopman, for joining us today on Mayo Clinic Q&A.



Narrator 18:08

Mayo Clinic Q&A is a production of the Mayo Clinic News Network and is available wherever you get and subscribe to your favorite podcasts. To see a list of all Mayo Clinic podcasts, visit newsnetwork.mayoclinic.org. Then click on podcasts. Thanks for listening and be well. We hope you'll offer a review of this and other episodes when the option is available. Comments and questions can also be sent to mayoclinicnewsnetwork@mayo.edu.