Zoom In on **Dementia & Alzheimer's**

The New Alzheimer's Drug: What is Kisunla?
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Transcript of Zoom with Paul Aisen, MD
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Please note: This transcript has been edited for clarity and brevity.

NANCY LYNN: Thanks and welcome, everybody. I'm Nancy Lynn from BrightFocus Foundation. BrightFocus Foundation is a 51-year-old organization that funds research globally for Alzheimer's disease, macular degeneration, and glaucoma. We've invested over 300 million over those 51 years in mostly young researchers. And we're really delighted that you're joining us today for the Zoom In on Dementia & Alzheimer's episode, "The New Drug: What is Kisunla?" And we have a ton to cover, so I'm going to run through quickly. If you can go to the next slide, Steve.

I should mention that the program is made possible in part by educational funding from Lilly, Eisai, Genentech, and Biogen. A lot of your questions this month were on the topic of Kisunla, which is great, but many were not. And so I just want to remind everybody that we've done a series of these on some of the other questions that you asked. They're free. They're available online. So if you want to know about how Alzheimer's is diagnosed or the outlook for clinical trials generally, and these are all online at brightfocus.org/ZoomIn. And this episode will be available in

about a week online as well. And I'll mention that we have added a series of episodes that focus on individual clinical trials. And we're going to give you the date for the next one of those at the end of this.

I'm going to introduce an excellent, excellent speaker today. Dr. Paul Aisen. Dr. Aisen Is the Epstein Alzheimer's Disease Director's Chair, at the Alzheimer's Therapeutic Research Institute, ATRI, and Professor of Neurology at Keck School of Medicine of USC. Dr. Aisen, who's been a long friend of mine and colleague, has been a leading figure in Alzheimer's disease research for nearly four decades. He has played a major role in our understanding of the continuum of Alzheimer's disease from the long pre-symptomatic phase through the eventual cognitive and functional decline. Dr. Aisen and his research team rigorously study new compounds, which may prevent the progression of Alzheimer's related brain damage and eventually offer prevention strategies for asymptomatic people. At the ATRI, Dr. Aisen coordinates and oversees the NIH funded Alzheimer's Clinical Trials Consortium, or ACTC. And that consortium now has 38 member sites across the country with extensive expertise in AD clinical trials. The mission is to accelerate the development of effective interventions for Alzheimer's and related disorders by coordinating shared expertise and utilizing centralized resources. Welcome, Dr. Aisen! We are truly delighted to have you today. And I'm going to start us off by saying we have a new drug approved by the FDA that is called Kisunla as its brand name, scientifically referred to as donanemab. What is Kisunla?

DR. PAUL AISEN: Kisunla is an effective disease modifying treatment for Alzheimer's disease. It is actually an antibody that is administered intravenously that attacks amyloid plaques. Amyloid plaques are a principal part of the Alzheimer's disease change in the brain. It is the first change that occurs in the disease, the accumulation of this plaque. And amyloid seems to drive the onset of Alzheimer's disease. The body is not able to get rid of amyloid. It's a glue-like substance. It sticks to the brain tissue and can't be cleared. The antibody, Kisunla, enters the brain and binds to this substance, to the amyloid, and enables clearance. It allows the body to be more effective in removing amyloid from brain. So treatment over time with this antibody removes amyloid from brain, and actually it's quite a dramatic effect. So we see amyloid using a PET scan. It's a brain scan that can show molecular changes in the brain, and

amyloid PET scans show us amyloid. And treatment with this antibody, with Kisunla, removes amyloid and can normalize the PET scan. It's not a subtle effect. It's a traumatic removal of a principal abnormality of Alzheimer's disease. So it's a very exciting development in our ability to address this disease.

NANCY LYNN: So what I'm hearing from you is it works, because that was the second question I was going to say. Does it work and how? But let's go to differences between Leqembi, which is the drug that was approved previously, and Kisunla. Similarities and differences. And we've had several questions about how would your doctor decide which one you would be on. We've also had some questions about if you are on Leqembi, could you switch to, not donanemab, Kisunla? Those types of questions. So jump right in.

DR. PAUL AISEN: Sure. So this has been an amazing year in Alzheimer's disease research. In the past one year, we've had two drugs fully approved that slow the progression of Alzheimer's disease. And it's something, yeah, we've been working on for many decades. And now finally in the past year, we have full approval of two drugs. The two drugs have a very similar approach to the disease. They both are antibodies. So antibodies are natural defense mechanisms against—

AUDIENCE: Question. Do you mean Alzheimer's disease, which can only, as far as I know, be diagnosed by brain autopsy? Or do you mean in general dementia?

DR. PAUL AISEN: I mean, Alzheimer's disease. And yes, it was true in the past that Alzheimer's disease could only be diagnosed at autopsy. That has changed. We now can diagnose Alzheimer's disease in living people with very high accuracy. And without getting too far off topic. The two ways that we do that are both ways of seeing amyloid in brain. One is using PET scans, which can now show us amyloid in the brain in living people. And the other is that we now have blood tests that can also show us the same thing. So these days we can accurately identify Alzheimer's disease in living people. And actually, that's part of the reason that we've achieved this success in developing therapy. Essentially, we can now see what we're doing.

So these two drugs that were both developed in the last year represent a huge step forward in Alzheimer's disease therapeutics. We've had treatments for many years, drugs like Aricept, that are effective and can improve memory in people with Alzheimer's disease. But those drugs, Aricept, memantine, and others, they're symptomatic treatments. They don't attack the brain abnormalities that drive the disease, the plaques and tangles. They boost memory by changing chemicals in the brain. What we have now with these two drugs in the past one year are drugs that are effective at removing one of the principal molecular causes of Alzheimer's disease, the amyloid plaque. And that means that they slow disease progression, something that the symptomatic drugs do not do. Symptomatic drugs have no effect on the overall course of Alzheimer's disease. These drugs, Leqembi and Kisunla, slow disease progression. They don't stop progression, but they slow disease progression by 30%. Is that a meaningful slowing? I think it's hugely meaningful. So if you want to think about what a 30% slowing means, well, if you were to treat someone for three years, that means saving a year. That means that if you are going to eventually lose the ability, say, to drive a car or to manage your finances down the road, then that would be delayed by a year over the course of three years of treatment. It's not enough. We need to stop the disease. We need to prevent the disease. But a 30% slowing is a very important benefit. And that's what we see with these two new drugs, both of which remove amyloid from brain. Having the two drugs together approved is essentially proof that removing amyloid is helpful, and it gives us great confidence that these treatments are changing the course of disease.

What are the differences between Kisunla, the new drug, and Leqembi, the drug that was approved last year? Well, they attack a different part of the amyloid molecule. And that has some implications for how they work. Leqembi has to be administered initially every two weeks intravenously. Kisunla is administered every month intravenously. So that's a difference. Kisunla works faster. So the removal of the amyloid occurs more quickly with Kisunla than with Leqembi. But the side effects appear to be somewhat greater with Kisunla, perhaps related to its faster removal of the amyloid. Removal of amyloid does come with side effects. And those side effects have to be monitored. And when those side effects occur, treatment may have to be suspended for a period of time or even stopped.

So these drugs have clear benefits. They also have risks. They need to be used by people who understand these drugs. But that caution aside, it's a major breakthrough and I think really has the potential to improve the lives of millions of people.

NANCY LYNN: I'm going to get into some of the nitty gritty. And I will get to the questions you all have put in. And Gloria, I will also get to you. I just want to get through a little more info from the questions that were pre-submitted. So who can prescribe? I have a question, for example, can a general practitioner prescribe this medicine? I've not been able to get in to see a neurologist. All the ones that I've been referred to are booked for a year. And I wanted to get that out, because I know so many people have this problem.

DR. PAUL AISEN: Yeah, it's a very important issue. Any clinician who can prescribe drugs can prescribe these drugs. So any physician, any advanced practitioner who can prescribe drugs can prescribe these drugs. However, as I've just said, there needs to be a good understanding of how to use the drugs, how to identify the right people to get the drugs, and how to monitor the treatment so that if there are side effects, they can be managed effectively. So what I'm saying is that any physician can prescribe these drugs, but not any physician should prescribe them without fully understanding how to identify the right people and how to monitor the treatment. We need more people with expertise. They are not going to just be neurologists. There are not enough neurologists to treat all the people that can benefit from these new drugs. So it is essential that the health care community gear up to be able to take advantage of these drugs with educational programs for clinicians that enable more people to be able to prescribe the drugs. And I'll have to say that it's not just the prescribing clinicians. We need expert radiologists to help us interpret the MRI scans that are used to monitor potential side effects. We need infusion centers because both of these drugs are given intravenously. So we need more infrastructure in the health care system to allow us to take full advantage of these new treatments. And a lot of work is being directed towards alleviating these bottlenecks. But yes, right now, the bottlenecks are still a big problem.

NANCY LYNN: Who is eligible to take the drug? Who are the right candidates to get this drug?

DR. PAUL AISEN: The drug, actually both drugs, have been proven to be effective at a stage of disease that we call early AD. Early AD is more specific than just meaning early in the course of disease. Early AD means this. Individuals who have a degree of impairment that we, clinicians, call mild cognitive impairment or mild dementia. These are people who have symptoms, symptoms of difficulty learning new things, difficulty with memory, difficulty with other aspects of cognitive function. They have some challenges in day to day tasks. But the challenges that they have functionally are relatively mild. It is this group of people that have been enrolled in the large definitive trials of Leqembi and Kisunla. And these are the people that are candidates for treatment now.

NANCY LYNN: And Richard just asked, the clinical data submitted for the approval of Kisunla seemed to indicate that it has a greater effect on people who are younger, under 75. Is that a factor to consider?

DR. PAUL AISEN: The trial data gives us a lot of clues, and some of them are not definitive. I will tell you that. I would recommend these treatments for people younger than 75 and people over the age of 75. We still have a lot to learn, and studies are ongoing to learn more. In general, we think that removing amyloid will be most effective at an early stage of disease. But some people who are over 75 are at an early stage of disease. Some people under 75 are at an early stage of disease. We think that the stage of disease is more important in predicting the benefit than the age. So, no, I would not just use these drugs in people under the age of 75.

NANCY LYNN: And I want to say that this sort of announces how important it is to try to get an early diagnosis of dementias. And Dawn from Saint John's, Florida had written, could you define early-stage Alzheimer's, since Alzheimer's is not often diagnosed early? So there is a catch 22 there. And it's really important to try to get a diagnosis. And we there is a Zoom In on how to get a diagnosis on our website.

DR. PAUL AISEN: I think that's a very important question, if I can just elaborate on that a bit. Historically, we considered Alzheimer's disease to be a dementia. Dementia means cognitive impairment that is bad

enough to interfere with your daily life. We've always known, though, that cognitive impairment was apparent to people even while they were still functional, still able to do activities of daily living. But we didn't make a diagnosis of Alzheimer's disease based on our own definition of the disease until someone had dementia, sufficient impairment to interfere with daily function. But that has all changed. Now that we have diagnostic tools that can show us at a molecular level what is happening in brain, now we can accurately identify people with Alzheimer's disease prior to the onset of dementia. And mild cognitive impairment is the term we use for people who have memory symptoms, and we know their memory is impaired if we do memory testing, but they still function pretty well and don't meet the criteria for the dementia syndrome. But we can be certain that they have Alzheimer's disease by doing an amyloid PET scan and seeing amyloid in brain or even now doing a blood test that shows amyloid in brain. So we now can accurately identify people with Alzheimer's disease before the onset of dementia. And it makes it that much more important, now that we have a treatment for people, and I've just said I think the treatment is likely to work best and the evidence so far suggests that it works best the earlier you start the treatment. It's just become very important for people with even mild symptoms to be evaluated. See if they have Alzheimer's disease, because if they do, there's something we can do about it.

NANCY LYNN: And Dr. Aisen, are there trials that are recruiting right now that people could participate in for people who are presymptomatic who might want to find out if they have amyloid and try to get these drugs earlier?

DR. PAUL AISEN: Yeah, so there are two large trials. There are two drugs that we have that have been approved at the early AD stage. And both of them are now being tested at a presymptomatic stage. What do I mean by a presymptomatic stage? I mean people who have amyloid in brain. And we know that on the basis of amyloid PET scans or accurate blood tests. And yet don't have any significant impairment. They don't have mild cognitive impairment or dementia. They are considered presymptomatic. We hope that removing amyloid in people before the onset of symptoms, but people who have amyloid in brain, the target of these therapies,

identifying people before the onset of symptoms and removing amyloid from brain at that point we hope will be more effective, have a bigger slowing effect on the disease process. That's being tested in two large trials, the TRAILBLAZER-ALZ3 trial, which is being conducted by Lilly, the manufacturer of donanemab or Kisunla. And the AHEAD trial, which is being conducted by our group in conjunction with Eisai, the manufacturer of lecanemab or Leqembi. These two large phase III trials are now testing the benefits of amyloid removal prior to the onset of symptoms.

NANCY LYNN: Thank you. That's awesome. I'm going to ask about three more questions, Gloria, and then I'm going to come to you and start reading out the questions in the chat box. But because we've gotten so many questions about this, what does it cost? Is it covered by insurance?

And the other one, which is not related, is a lot of folks are asking if they are APOE4 positive, if they have a different type of-- if they've been diagnosed with a different type of dementia, are they candidates for this drug? So let's start with what does it cost and is it covered by insurance? And also, are the tests covered by insurance, et cetera?

DR. PAUL AISEN: So the simple answer is yes. The drugs are covered by insurance and the testing is covered by insurance, because these are full approvals of these two drugs. CMS is the government agency that decides whether Medicaid and Medicare cover a drug. CMS has already decided to approve and pay for a treatment with Leqembi, the drug that was approved last year, and will certainly also cover treatment with Kisunla and the tests necessary to identify who is a candidate for treatment. So, yes, they're covered. That's a good thing, because they are both expensive. The costs for the drugs themselves are around $30,000 a year. And that's not including the costs of the intravenous infusions, the diagnostic testing, the monitoring with MRI scans. The costs are quite substantial, but they are being covered and will be covered by Medicare and by insurance.

NANCY LYNN: And the question of whether these are effective or have a different effect in folks who are APOE4 positive or have Lewy body or frontotemporal dementia or other types of dementias.

DR. PAUL AISEN: Let me answer the second part first. Dementia is a syndrome. Cognitive impairment interfering with daily function. Dementia

can be caused by many things, including strokes and other abnormalities in brain like Lewy bodies. Lewy bodies are another type of deposit that can occur in the brain with aging that can also cause dementia. These antibodies attack amyloid. Amyloid is not part of these other dementias. So these drugs are only going to work if you have amyloid in brain and if the amyloid is driving the cognitive symptoms. So they're only going to be effective in people who have an amyloid disease, and that's Alzheimer's disease. But I will say that many times these other causes of cognitive impairment, vascular disease and Lewy body disease, many times they are accompanied by amyloid plaques and Alzheimer's disease. So it's not so straightforward. If there's amyloid in brain, there's a target for these drugs. But these drugs have only been tested in people with a diagnosis of Alzheimer's disease. Those are the people who should be treated now. But additional studies are now being done to evaluate the potential benefits of these treatments in people who have multiple etiologies, multiple factors causing cognitive impairment. So these are very important questions that are still being addressed. But right now it's people with a diagnosis of early AD, meaning mild cognitive impairment or mild dementia, associated with amyloid in brain that are candidates for treatment.

Now, the other part of the question was about APOE. APOE, I think most people know, is the most important risk factor, genetic risk factor, for the sporadic, the most common type of Alzheimer's disease. Roughly 2/3 of people with Alzheimer's disease have at least one APOE4 allele gene. Everybody has two copies of APOE, and you can have 1, 2, or 0 copies of the E4 type. And the more copies you have, the higher the risk is that you will develop Alzheimer's disease. But about a third of people with Alzheimer's disease don't have any copy of E4. And a significant portion of people who don't have Alzheimer's disease do carry E4. It's a risk factor, but it's not a one to one relationship with the disease. Now, in these trials of both Leqembi and Kisunla, 2/3 of the participants had E4. There were benefits in people with E4 and without E4. One thing I will say is that the risk seems to be greater in people with E4. The drugs seem to be safer in those people with early AD who don't carry E4. But the benefits outweigh the risks in our view and in the language of the approval in all people with early AD. But in my opinion, people should consider their genetics when they are evaluating the treatment, because the expected results of this

treatment are different depending upon your genetic background. And in particular, people with two copies of the E4 gene have a significantly higher risk of side effects from these treatments. So that has to be part of the discussion, part of the consideration of treatment between clinicians and patients and families, what the risk based on APOE is. So again, I think that everybody with early AD is a candidate for these treatments, but I think that genetics should be part of the discussion about whether to use them.

AUDIENCE: My question is, what do we do as patients?

DR. PAUL AISEN: So first of all, this is definitely a problem. And this disease can be challenging. Obviously, it's horrible for patients and families. It's challenging for clinicians. Many doctors are not fully educated about this disease. We don't have enough neurologists to evaluate people and manage this disease. So again, we need to improve our health care infrastructure to take full advantage of these treatments. But I do want to say that, in my opinion, people who have symptoms, people who have mild cognitive impairment or mild dementia, definite evidence of cognitive impairment that is at the stage of early AD that would be appropriate for treatment, those people should have testing to see whether they have amyloid. People who have no symptoms may have amyloid. We are studying whether these treatments are beneficial in people with no symptoms. We don't have the answer to that yet. But I think it would be reasonable for a clinician to say, well, since we don't know that there's an effective treatment, it may not be worth the substantial expense and trouble of getting a PET scan in someone with no symptoms simply on the basis of a family history. But someone with symptoms, in my opinion, should be tested, because the benefits of these treatments for early stage symptomatic disease are considerable. So again, speaking in general terms, someone with mild cognitive impairment, in my opinion, should have evaluation of whether there is amyloid in brain with PET scans and/or blood tests to see whether this treatment should be used.

NANCY LYNN: Let's talk about where somebody in Gloria's situation can go. We had a question from YouTube. Which medical centers have the

most experience with these two drugs, have treated the most number of patients? And this is a critical problem in the country right now. You're absolutely right. There is a huge disconnect between the scientific advancements with these drugs and the doctors, the whole field in actually knowing how to use it. And so the field, I should say, is very well aware of this. And I think programs like this one should actually be shown to doctors and neurologists as part of an education program. And there's many, many folks working on this, but we have to catch up now. So I would go back to Dr. Aisen to talk about where people can go. Where there are Alzheimer's Disease Research Centers? What are other avenues, Dr. Aisen?

DR. PAUL AISEN: Yeah. So just taking Keck as an example. Keck at USC in LA has an Alzheimer's Disease Research Center. That is a place of outstanding expertise and experience, including experience with treatments like these. It took a while for Keck to gear up for using this treatment. But I would say Keck is now administering these drugs. So perhaps not Kisunla yet, which has been approved only two weeks ago. But Leqembi, which was approved a year ago, is now available for treatment in LA, including at Keck. And I think that people should pursue treatment. And even as the infrastructure gears up, and I am sure there are waiting lists, and I don't have a ready solution for that. But yeah, I think people who have mild cognitive impairment or mild dementia should be evaluated for the presence of amyloid to see whether this is an appropriate avenue for slowing disease down. And I think ADRCs, Alzheimer's Disease Research Centers, which are at about 35 places around the country, including Keck, those are great resources. Now, that doesn't mean they have solved this bottleneck problem. But those would be great places to go. In general, the sites that have been involved with the testing of these drugs are great places to find experienced clinicians. And again, that includes the ADRCs, most of them, but also other leading medical centers in big cities. It's harder when you get away from big cities. And it's even a greater bottleneck to getting the availability of these drugs. So I believe this is a big problem. Having two drugs on the market is going to help us drive growth in the infrastructure more effectively. So I know this will get better, but right now there are still substantial bottlenecks.

NANCY LYNN: There definitely are. And how long does someone need to be on Kisunla or Leqembi?

DR. PAUL AISEN: Well, in the clinical trials that proved the benefit, treatment was for 18 months, for a year and a half. There's still a lot of debate on exactly how to decide how long someone should be treated. Just because a trial was 18 months, that doesn't mean that the drugs only work for 18 months. And in fact, the assumption would be that these drugs work throughout the period in which they were studied. That is mild cognitive impairment and early AD. So there is some experience with long term treatment beyond 18 months, but I would say that that's still a relatively limited experience. But my own view would be that for someone who has MCI and early AD who tolerates the treatment, and again, the treatment has to be monitored because there are side effects. And in rare cases, those side effects can be quite severe. But in someone who tolerates the treatment, I would say that treatment is appropriate throughout the mild cognitive impairment and mild dementia stages that were studied in these trials.

DR. PAUL AISEN: One of the differences between the two drugs, Leqembi and Kisunla, is that the makers of Kisunla, Lilly, have felt that the drug could be stopped earlier. And in fact, some people in the phase III trial of donanemab, Kisunla, stopped treatment because their amyloid scans, their amyloid PET scans became normal. And it is the view of Lilly that it may be appropriate to stop not only at 18 months, but before 18 months. Just monitor the amyloid PET scan. And when it becomes normal, stop treatment. That approach is controversial, and some experts in the field wonder whether benefits would be greater if treatment was continued longer. So I will just say it's a very important question for which there is no clear answer. Leqembi, the older drug, was not stopped in people whose amyloid PET scans became negative. But in the study of Kisunla, people were stopped when their amyloid PETs became negative. And we're still studying what the right guidance should be for patients and for clinicians. We'll learn more in the coming months and years. But right now that's still an open question.

NANCY LYNN: There's an interesting question in the chat from Samuel. How long after being on the drug will patients be able to discern improvement? And I think it's an interesting question, because it's not

exactly improvement that will be discerned. So can you answer that?

DR. PAUL AISEN: Yeah, so if someone with mild Alzheimer's disease dementia were to start a drug like Aricept, that's a symptomatic drug that boosts memory a bit, they would potentially notice the benefit of treatment in about 12 weeks. So three months. That's a symptomatic effect. And again, that drug has no effect on the course, the decline over time of the disease. Leqembi and Kisunla are disease modifying drugs, not symptomatic drugs. We expect no benefit to be apparent for 12 weeks or even 24 weeks, because what these drugs do is not to boost memory. They slow the rate of decline. And that becomes more apparent the longer the time of observation. So I would say by about a year, you can tell the difference between a group of people on these drugs and a group of people not on these drugs, because the decline has been faster in the people not taking the drugs. But people taking the drugs are not improving. Their rate of decline is slowing. And so it's quite difficult for them to judge the benefit. We know the benefit from doing clinical trials and comparing groups, but individuals are not going to see a benefit in 12 weeks, as with Aricept, or even 24 weeks. The decline is slower over time and is measurable and definite by about 12 months to 18 months. So it's a very important question.

NANCY LYNN: And Britt asked, are there any programs in place or planned to track, measure, and study these treatments alongside lifestyle interventions and health metrics management? It seems that might multiply the benefits of the treatment and provide maximum results. And I think that's interesting. What do you see for the future in terms of combining these treatments with lifestyle improvements and other types of treatments?

DR. PAUL AISEN: Yeah. So first, let me say, as I said at the outset, that we're not done here. The benefits that we get from these treatments, about a 30% slowing, that's not enough. It's important. It's valuable, and it's not enough. So how can we do better than that. I think combination therapy is an important strategy. Now, one combination approach would be to add additional medications. And we are actually launching a big study now that combines anti-amyloid treatments with anti-tau or anti-

tangle treatments. And we think that's one way to try to increase the benefit. But absolutely, I agree that—

NANCY LYNN: Sorry, Dr. Aisen, what's the name of that study?

DR. PAUL AISEN: That study is the Alzheimer's Tau Platform study. But it's important to consider other interventions as well. And there is a study that's still in the funding stage, so it's not definite that it's going to be funded, but that combines amyloid removal with other interventions, including lifestyle interventions. There are other studies planned that address amyloid accumulation as well as the accumulation of other pathologies, like Lewy bodies. So there are a lot of efforts to combine both lifestyle and pharmacological treatments with amyloid removal, and these are all important. So I am also an advocate of combination approaches. Again, the two biggest ways we have, I think, of increasing the benefit are combination therapies and earlier intervention, and we are actively pursuing both strategies.

NANCY LYNN: Would it be acceptable to take these therapies along with symptom improving drugs? Someone also asked about the Exelon patch in the pre-submitted questions. It's fixing what we have already.

DR. PAUL AISEN: So right now the symptomatic drugs are approved therapies that are widely used in people with a mild dementia stage. The mild dementia stage is also a stage for which Kisunla and Leqembi are approved. And I think at that stage, it makes perfect sense to combine symptomatic treatments with amyloid removal treatments, Kisunla and Leqembi. In the mild cognitive impairment stage, the benefits of the symptomatic treatments are less certain, but many people take these drugs at the MCI stage as well, and I do not see a problem with combining them at that stage with amyloid removal either. So I think it is reasonable to use the new drugs in combination with the older symptomatic treatments.

NANCY LYNN: And Samuel asks, is brain shrinkage altered by Kisunla?

DR. PAUL AISEN: That's an interesting question with a somewhat complicated answer, but I'll try to be brief and summarize. Brain shrinkage

is inevitable with aging. Brain shrinkage is worse in people who have Alzheimer's disease. So the brain shrinks more than people who don't have Alzheimer's disease. The shrinkage in Alzheimer's disease is not fully understood. It seems to be an accompaniment of neurodegeneration, the degeneration of brain cells and synapses. When you remove amyloid, though, with a drug like Kisunla or Leqembi, you are not only removing amyloid, but you're removing the tissue response in the brain to the amyloid. And in general, amyloid removal actually causes a little bit more shrinkage than people who are not on these drugs. That does not seem to be harmful and it does not interfere with the benefits of treatment and most likely has to do with a quieting of the tissue response, like the inflammatory response to the plaque. Inflammation is generally associated with swelling, including swelling in the brain, and that is lessened by removing the amyloid. But on an MRI scan, which is the usual way we measure atrophy, there's actually a little bit more atrophy in people on treatment than people not on treatment. Again, doesn't seem to have anything to do with the beneficial response. The beneficial response is there in people with this slight increase in shrinkage. So it's not a straightforward answer, and it's been somewhat confusing to scientists, but doesn't seem to be important with regard to the clinical benefit of these treatments.

NANCY LYNN: And there's a lot about Alzheimer's and other dementias that's confusing to scientists still. And I think Dr. Aisen would be the first to recognize that. Since we have 10 minutes left, can you talk a little bit more about the side effects and the management of the side effects? How much of a concern? Well, let's talk about what the side effects are and how much of a concern they are. And can that concern really be mitigated by monitoring them carefully?

DR. PAUL AISEN: Yeah, so Leqembi and Kisunla, as I said, are antibodies that attack amyloid in brain. And when they attack, they essentially bind to the abnormal chemicals in the brain and enable the body's natural defenses to become effective against those abnormal deposits. And the abnormal deposits are then cleared by scavenging cells in the brain, and they're cleared through the vasculature, the blood vessels in the brain. As the amyloid moves out, there can be a reaction in the small blood vessels

to the removal process. And that reaction can cause areas of swelling. And it can cause what we call microhemorrhages, tiny areas of bleeding. So the side effects that are related to amyloid removal are swelling and tiny microhemorrhages, tiny areas of bleeding in the brain that accompanies this treatment.

How often does this happen? Well, it happens in a significant portion of people who are on these treatments, ranging from about 15% to 25%. So from, say, one in six to one in four people who are on these treatments will develop these adverse effects, swelling or microhemorrhage. In the majority of people who have these effects, they don't know it, and the effects just go away, even with continued treatment. So most of these events, most of the events of swelling and microhemorrhage, are actually inconsequential. People don't know about them, and they go away. But in some cases, they cause symptoms. And those symptoms, the most common is headache. But they can also cause neurological symptoms, because they're indicative of abnormalities in the brain. And they can occur in different parts of the brain and cause different types of symptoms. There can be some confusion. There can be some unsteadiness, some visual symptoms. They can cause neurologic symptoms. And typically, those symptoms just resolve. But in some cases, the symptoms can persist and can become serious. In very rare cases, they can become life threatening. And the most serious type of symptom is significant bleeding in the brain. Tiny areas of bleeding in the brain usually are inconsequential. But in rare cases, there can be significant bleeding in the brain, and that can be life threatening. How often does that happen? Not often. Something like 1 in 1,000. But it is a potential risk.

What do we do about these risks? Everybody who is treated with these drugs should be monitored with MRI scans to look for evidence of swelling or bleeding in the brain. Because if we see evidence of this, we can adjust the treatment. For significant abnormalities, we can stop treatment. For moderate abnormalities, we can pause treatment for a period of time. We can make adjustments to diminish the possibility of severe cases. So what I'm saying is that everybody who is treated with Leqembi or Kisunla should have multiple MRI scans. And there's a schedule of scans that they should have. The first one might be six weeks

or so after starting the treatment and then several scans during the first six months to monitor these side effects. And the reason for that is to allow adjustment of dosing schedule and to minimize the likelihood of severe consequences. So everybody on these drugs should be monitored with MRI scans. And every clinician who treats somebody with these drugs must be familiar with this type of adverse effect.

NANCY LYNN: And I'm going to ask one more question from the chat from Dean. Can you please talk more about the considerations doctors will weigh in deciding which of the two drugs to prescribe to a given patient? Will it really work like that? Will it depend on the patient's condition or will it depend on what they know best or how will that work?

DR. PAUL AISEN: So first of all, what I would say is these two drugs are more similar than different. And if someone is taking Leqembi and they're thinking, well, now there's a new one. Should I switch? My answer would be no. They're similar. If someone is not taking either drug and they are both available, I mean, if only one's available, I would say go with that one. If they are both available, how do you decide between them? Well, a knowledgeable clinician would review the differences with patients and families. And what are those differences? Well, right now, Leqembi is an intravenous infusion every two weeks. Kisunla is once a month. That's a difference. That difference favors the new drug. The risk of the events I've been talking about, the swelling and the bleeding, seem to be higher in the new drug than in the older drug. So safety considerations might favor Leqembi over Kisunla. And so the discussion, if both are available, would be around these differences. Kisunla seems to remove amyloid faster. That would sound like a good thing. But the faster removal is probably why there seems to be a higher incidence of side effects. So the best that a clinician can and should do is to review these differences and decide together with patients and families which they would prefer to try. The two drugs have not been compared head to head. So certainty would be impossible on which drug would be better for any individual. But discussing the differences that we see should be involved safety considerations, convenience considerations. That might help make a decision.

NANCY LYNN: I want to wrap up by talking about there's sort of an overarching-- not sort of. There is an overarching, tremendous frustration for people who have Alzheimer's in their families who have a loved one who are joining calls like this. Certainly, there's been little to hope for in the past, and the system is very difficult to navigate, as we're hearing from Gloria and so on. And these are very real issues. But that said, Dr. Aisen, I've been doing this about 15 years. You for much longer. I'd love to leave us on a note about how far we've come and how at this point, while there's real issues, and I'm saying this because I want everybody to know that we share your frustration. Most of us who do this for a living in some way, shape, or form have Alzheimer's in our family. Most people have Alzheimer's in their family or have had something related. So we share very deeply the frustrations inherent in the health care system and in particular in treatments of dementia. But how would you wrap up the incredible joy that the field feels after four or five decades of not much progress that now there are blood tests. There are two disease modifying drugs. There are hundreds more clinical trials taking place for other drugs. So, Dr. Aisen, give us some hope about this moment in history and the few next years to come within our lifetimes.

DR. PAUL AISEN: So what I would say is that it's tremendous the progress that's been made that we now know that we can slow this disease down. We know that we can remove the amyloid that is driving this disease. We have a lot to learn. We need to build on the success. But the fact that we are now on a road to controlling Alzheimer's disease is absolutely clear. Whereas we struggled with failure after failure for decades, and now we are on the path of success. We have to build on what we've learned from these two drugs. We have to continue to study them, to study combination treatments, study early treatments. We will get better and better in our ability to slow down the disease. But knowing that we can do it, now we know, knowing that we can do it, it's just fabulous and exciting and it's invigorating the entire field, the pharmaceutical industry, the academic community, funders, philanthropic groups. Everybody is energized by this success. We are going to make steady progress moving forward, and we are going to control this disease in the coming years.

NANCY LYNN: Well, if I was ready, I would want you to be my doctor. Do

you see patients at Keck?

DR. PAUL AISEN: I no longer see patients. I am a full-time research scientist. So I appreciate that comment, Nancy, but I do not see patients. All my time is on research.

NANCY LYNN: Well, and some people have asked that question in the chat, but I'm agreeing with them. But if they wanted, they can try to go to the ATRI and see people that have been trained on your team.

DR. PAUL AISEN: So ATRI is a Research Institute. We conduct clinical trials and we work on methods for clinical trials. But at Keck, there is a Research Center, the ADRC, that evaluates people and does offer treatments. So yes, those treatments are available, but we are a research program. ATRI is research.

NANCY LYNN: I want to thank you so much. And I want to get you to agree to come back while all these people are witnessing, because the way you explain things is extremely understandable. And it's such an exciting time. And I'll just say we also in the field have watched you work hard for decades. And it's tremendously gratifying that you're willing to share this expertise with the public. So, Steve, I'm going to ask you to pull up our closing slides. For those of you who are interested in learning more about Kisunla and Leqembi, these are the websites and the numbers on the screen here that you can reach out directly to the companies and to find out who is prescribing these. They will be able to help lead you to these medications. So we will be sending this in about a week with the recording of the show. And so you will have this. Or you can take a picture of the screen now, but we will be sending you these resources. If you'd like other publications about Alzheimer's disease for free, you can email info@brightfocus.org. And all of our resources in English and in Spanish are available at brightfocus.org. For these episodes, again, there's a lot of episodes that relate to what we were discussing today, but go in depth on other subjects. They're available at brightfocus.org/zoomin. Next slide, please. If you have suggestions for future topics, you can email us at reply@brightfocus.org. And next slide, please.

The question about brain shrinkage I find very interesting, because on

August 1st, we're actually having somebody on who's going to be talking about the HOPE study in case anybody is interested in looking at that in advance and would like to join on August 1st. And the HOPE study is trying a completely different type of technology than the therapeutics we're talking about today. It's actually a neuromodulation headset that's using light and sound and different kinds of waves to see if they can affect the neuronal damage and brain shrinkage that happens in Alzheimer's. And that trial is currently recruiting. So if you're interested in learning more about that, join us on Thursday, August 1st at 1:00 PM ET, 10:00 AM PT. And then the next regular episode will be on September 19th. Alexa's writing to me, you can sign up for the program for each month on our website.

And I'm going to close out today just to say, again, thank you so much, Dr. Aisen. We deeply appreciate your time. And thank you all also for participating in bringing us your time and Gloria for speaking with us openly. And I have in the chat, haha, yes, have him come back. Have him come back. So we will do that. Thank you all. I hope you have a great day. And don't hesitate to email us with thoughts, suggestions, topics, questions. We're delighted to be here for you guys. So thank you on behalf of BrightFocus Foundation and our sponsors. Have a great day.

Resources

BrightFocus Foundation: (800) 437-2423 or visit us at BrightFocus.org. Available resources include—

- Kisunla (donanemab-azbt)
    - https://www.kisunla.lilly.com/
    - 1-800-LillyRx (1-800-545-5979)
- Leqembi (lecanemab-irmb)
    - https://www.leqembi.com/
    - 1-833-4-LEQEMBI (1-833-453-7362)
- Treatments for Alzheimer's Disease Fact Sheet
- Alzheimer's Disease Research Centers (ADRCs)