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Updates in the Management of Early Alzheimer's Disease

Announcer:
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Here is Dr. Richard Isaacson

Dr. Isaacson:
Did you know that between the years of 2000 and 2018, deaths from heart disease decreased by 7.8%, while deaths from Alzheimer's disease have increased by 146%?

Dr. Agronin:
That's a really stunning figure. This change is probably due not only to increasing numbers of people who have Alzheimer's disease, but the bottom line is just we have a greater recognition of the role that Alzheimer's disease plays in people's deaths as well.

Dr. Isaacson:
Today on Clinical Countdown, Alzheimer's Disease Edition, we're taking a closer look at the clinical trial landscape and limitations of the current standard of care. You ready, Dr. Agronin?

Dr. Agronin:
I'm ready to go.

Dr. Isaacson:
So let's dive right in. Dr. Agronin, could you please take us through some of the important aspects of the Alzheimer's disease clinical pipeline and the most recent clinical trial data?

Dr. Agronin:
Absolutely. I would say, in a word, immunotherapy. That's really the main approach. Trying to find ways to use our own immune system to get rid of the toxic beta-amyloid and tau proteins in the brain, which we believe are the main causative agents for Alzheimer's disease. So, right now, the really – the hottest topic is aducanumab, which is an anti-amyloid antibody focused on the aggregates of beta-amyloid in the brain. You may be aware of some of the controversy, going back about 10 months ago. There was a decision not to advance with aducanumab. A subsequent review of the data showed that individuals who were on it longer at a higher dose did appear to have a significant slowing in terms of their course, and so aducanumab actually is now being reviewed by the FDA.

In addition to that, we also have BAN2401, which is another anti-amyloid immunotherapy which is being studied. There are also several anti-tau immunotherapies being studied. You know, one of the beliefs is that as bad is amyloid is, tau is even worse. And that may be really the main destabilizing force in terms of causing damage to brain cells and circuitry in the brain. So we have a ways to go in terms of those trials, but those are probably some of the most active trials and perhaps some of the most promising.

There's a number of other agents being studied right now in clinical trials, for instance, you know, ways to either have a neuroprotective effect or to boost metabolism. You know, in the end, we're just trying to find some way to slow down the course of this disease, to modify its course to make a difference in the lives of so many individuals who are suffering from it today.

Dr. Isaacson:
That was great. And I'd like to add one more thing, that what we're realizing is that the earlier we treat, the more likely it is that the better the patient will do. So the exciting part about these anti-amyloid therapies is that we're really starting earlier, in the pre-dementia phases, in fact. The "mild cognitive impairment due to Alzheimer's" phase, which is where someone has mild memory complaints, but they can still, for the most part, take care of themselves. So whether we treat with anti-amyloid therapies or tau, or other mechanisms, you know, fighting against the inflammation or even neuroprotection. These are all of the different types of pathways that we're going to study over the coming years. And what I think what may happen, just like any chronic disease, like high blood pressure or diabetes or high cholesterol, this will be a combination of therapies, including lifestyle interventions, as well as multiple different, drugs that will hopefully one day get approved, so we can have comprehensive care for patients.

Dr. Agronin:
Yeah, Dr. Isaacson, I couldn't agree with you more. That's really the future we're looking at. And I wonder if you had any reflections on, you know, what's on the market now? The current treatments for Alzheimer's disease and what's the state in science for them now?

Dr. Isaacson:
Yeah, so based on meta-analyses, I do think that the current available FDA-approved therapies do have modest benefits, but they're only symptomatic benefits. The key take-home point here with the immunotherapies is these are DMTs or disease modifying therapies. So the goal is to not just have a symptomatic therapy, but to also do something to bend the curve, to slow disease progression, to delay the progression, the more severe phases of dementia, and that's when our patients can really be served in the best light.

Dr. Agronin:
Yeah, I think that's true. I would point out the 2 major factors that really get in the way here. First of all, too few people get diagnosed in the first place. And when they do get diagnosed, it's often so far down the line that you're not going to see the same efficacy for treatments. Or frankly, it may be too late for them even to get involved in a clinical trial. And so we just have to be better at these early diagnoses and better, as we'll talk about, in terms of using biomarkers. The other thing is that the average person with Alzheimer's disease has so many other comorbid factors. And I don't mean just medical issues, but psychiatric issues – depression, anxiety, behavioral issues – and those really confound getting people into treatment. It interferes with care at home; it decreases function. To get at these diagnoses and get these comorbidities treated, the better people are going to do in the long run.

Dr. Isaacson:
Yeah, and I agree. Throughout the stages or the phases of the Alzheimer's disease spectrum, there are absolutely things that we need to do. The first thing – I agree with you – we need to do is get a diagnosis in the first place. If we don't think about Alzheimer's disease as a condition that honestly starts in the brain decades before the first symptom of memory loss, we're going to not realize that we need to think about these things early. The initial, symptomatic phase of Alzheimer's disease is mild cognitive impairment due to Alzheimer's. That's when a person has mild memory complaints, but they can still take care of themselves. Further, to more definitively be proven that a person has MCI, or mild cognitive impairment due to Alzheimer's, we need to have some sort of a biomarker scan. So when someone is in the mild to moderate and also the moderate to severe phases of dementia, we have cholinesterase inhibitors that can be prescribed, and then in the more moderate to severe phases, we have a NMDA antagonist that can be prescribed that's in combination with an acetylcholinesterase inhibitor.

So while we do have some symptomatic therapies now, I'm very excited by the future. And I think we always have to think about both the pharmacologic treatments as well as the non-pharmacologic treatments. You know, the comorbidities that you mentioned, such as depression, anxiety, behavioral issues – we don't have a specific FDA-approved therapy just yet. Maybe one on the horizon to help with some aspects of behavioral disturbances, but there are things we can do, both from a pharmacologic and non-pharmacological perspective, to treat these, you know, both medical as well as psychiatric comorbidities.

Dr. Agronin:
Very true. It all starts with getting to the basics of how are we going to identify these individuals in the first place and follow them over time, because that's really where we have to start. You know, if you look at clinical guidelines now, you have to make sure that we have a really good clinical history, so we identify what's changing over time. That's really key to know what's normal, what's not. There are a lot of different screens out, like the Mini-Mental State Examination, the Montreal Cognitive Assessment, and others. And those are really good for triaging individuals and at least establishing a need, but they're not going to make a diagnosis. Even with a clinical history, lots of different conditions can resemble one another, so you need that information, but you can't stop there.

Dr. Isaacson:
Let's cover another important topic today by looking at the recommendations from clinical guidelines. Dr. Agronin, can you please tell us about some of the clinical guidelines surrounding the early diagnosis, imaging, biomarkers, and genotyping?

Dr. Agronin:
Sure, these are really important. So you have to begin with a clinical history, and to me, the main clinical pearl is look for change. What's changing over time, what degree? If you don't have that clinical history, it's hard to make an early diagnosis. There are really good screens, like the Mini-Mental State Examination, the Montreal Cognitive Assessment. They will help in terms of triage. They're going to give you a signal, but you're not going to use them to make a diagnosis. You really need to get more extensive neuropsych testing.

In terms of biomarkers that we look at, we start with some neuro image. And we prefer an MRI over a CT because you're going to get better resolution, especially looking for white matter changes, looking for atrophy in the hippocampus, which is going to really be suggestive of early Alzheimer's disease. We also have in this era of biomarkers the use of PET scans. So FDG PET scan, for instance, shows glucose metabolism in the brain. And we look for this common loss of metabolism in both parietal lobes, which is indicative of Alzheimer's disease. Now we have anti-amyloid therapy out, and in those research studies, we've developed both amyloid-based and tau-based, PET scans. The amyloid-based scans are on the market. The tau-based scans aren't yet. But the bottom line is if you find a high burden of amyloid or tau in these scans, that's really suggestive of a much higher risk that this is Alzheimer's disease.

Finally, we have genetic testing. There's the apolipoprotein E4, or ApoE4, as we call it, genetic marker. If you have one or two copies, you have an increased risk of Alzheimer's disease and sometimes indicative of being less responsive to treatment, having a worse course. Practically speaking, we often don't change treatment based on whether someone is ApoE4 positive or not outside of research studies, so we don't routinely check for that in clinical practice, but again, it's very relevant to research studies.

Dr. Isaacson:
Yep, and I agree that doing a comprehensive clinical history and then using that history to inform the workup is truly critical. You know, checking for reversible causes of cognitive impairment. We don't find this too often, maybe 5% of the time, but a B12 deficiency, a thyroid problem – these are things that, again, don't happen too frequently, but we want to make sure to rule them out. Also screening for depression. Pseudodementia of depression is something that's key and that's treatable. I agree completely with an MRI. It just gives better resolution in looking for temporal lobe atrophy, other aspects, parietal and sometimes frontal. And of course, using a biomarker scan or even spinal fluid measures are really the key things to more definitively diagnose. When it comes to the ApoE test, I think I agree. For diagnosis, it's just not very helpful. Because if you have an E4, you may not get Alzheimer's, and if you don't have an E4, you can still get Alzheimer's. So I do think that maybe in the future, when we talk about personalized medicine and precision medicine, especially someone earlier in the course before symptoms, maybe using ApoE4 to personalize care can be warranted, but not necessarily for sure in the diagnostic process.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Richard Isaacson, and here with me today is my friend and colleague, Dr. Mark Agronin. We're discussing the clinical trial landscape of Alzheimer's disease.

Dr. Agronin, I think you'd better brace yourself, because we're now moving on to lightning round. This section should be quick and pithy for each topic. You're up first.

Dr. Agronin:
I'm ready to go. So first question is what patient should be screened for early Alzheimer's disease? I would say anyone 55 and above who has any noticeable cognitive changes absolutely needs to be screened. Anyone 65 and above who even has subjective concerns, I think it's worth getting them screened. The basic thing here is that age is the index of suspicion, so the older you get, the more we need to intervene and get an early screening done.

Dr. Isaacson:
And I absolutely agree with you, and I really believe that an earlier diagnosis is the way we're going to fight and win the battle against Alzheimer's disease. Why is it important to make an earlier diagnosis? Well, because Alzheimer's disease begins in the brain 20 to 30 years before the first symptom of memory loss begins. And that leaves some time, some ample time or a window of opportunity to intervene. If we can diagnose in the pre-dementia stages, specifically the "mild cognitive impairment due to Alzheimer's" phase, and that's when we can introduce disease-modifying therapies, I think really that's when we're going to have the most chance for benefit.

Dr. Agronin:
Agreed. And in terms of which diagnostic tests are going to be most relevant, I would point to – basically, 3 are the most important. First is somewhat of a short neuropsychological assessment – longer than a screening exam. Something like the RBANS [Repeatable

Battery for the Assessment of Neuropsychological Status] is really good. It takes a little over an hour to do, and you get a full spectrum of data in terms of objectively what's happening. Second, you need a neuro image, like from an MRI, to mostly rule out problems that could be causing cognitive changes but just to get that basic assessment of what's going on in the brain. And finally, some form of a PET scan, either a functional scan, like FTG PET or an amyloid-based scan. But that's going to tell us relatively high risk factor or not for Alzheimer's disease.

Dr. Isaacson:
Well, this has certainly been a fascinating and educational conversation. But before we wrap up, Dr. Agronin, can you share with our audience your one take home message from today's discussion

Dr. Agronin:
Early assessment is key. It's going to identify risk factors, it's going to show potential symptoms, give you clues about causes, and it will help you get started with some form of treatment.

Dr. Isaacson:
Yeah, and, you know, from what I see is I just feel a lot of hope when it comes to the field of Alzheimer's disease. You know, we are currently limited. We have, you know, a handful of symptomatic therapies. They're FDA-approved. They work modestly, but they're the gold standard, and we use them every day. But the future is disease-modifying therapy, and if we can intervene before symptoms one day, or even when symptoms are just beginning, I think that's when we have the most chance for benefit.

Well, unfortunately, that's all the time we have for today. So I want to thank our audience for listening and thank you, Dr. Agronin, for joining me and for sharing all of your valuable insights. It was really great speaking with you today.

Dr. Agronin:
Dr. Isaacson, thank you so much. I wish all the listeners the best of success with their clinical care.

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