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Differences Among Agents

Announcer:
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Dr. Agronin:
This is CME on ReachMD, and I'm Dr. Marc Agronin. I'm here today with my colleague Dr. Richard Isaacson.

Dr. Isaacson, immunotherapy is a big topic right now. Let's talk in detail about some of the different agents being used in immunotherapy. What are, if any, meaningful differences between them? Let's talk a little bit about safety. And basically provide an orientation to the specific agents.

Dr. Isaacson:
Yeah, so when it comes to immunotherapy and the anti-amyloid agents, you know, this is a field that's been, you know, it's a 20-year field, believe it or not. I think most people aren't aware that we've been assessing from AN-1792, you know, that was 20 years ago, to the earlier days of bapineuzumab, and nowadays we talk most about aducanumab, which was the first FDA-approved, anti-amyloid drug and disease-modifying therapy, and then lecanemab and donanemab, which are basically now going to be reviewed by the FDA. You know, we've really gone through a variety of agents. And the take-home point with these agents is they're all anti-amyloid drugs, but they attack different things, whether it's oligomers or protofibrils, or they're IV once a month or twice a month or subcutaneous. Gantenerumab was a drug that was being studied subcutaneous, for example, and that drug did not move the needle, did not have better clinical outcomes. And so that didn't really pan out. So other drugs that were used, bapineuzumab, for example, ages ago, that drug wasn't probably used in everyone that had amyloid in the first place. And maybe it wasn't used at the right dose at the right time, it was used too late in the course of the disease.

So the take-home point with these drugs is there are meaningful differences between the agents; some work and some don't because of the exact type the pathway that they attack. And it's also because earlier and earlier we go in this disease now. Now we attack Alzheimer's when it's in the mild cognitive impairment due to Alzheimer's stage rather than years ago when we've looked at people with mild, moderate, even more borderline severe Alzheimer's disease, when they've had amyloid for ages. So the take-home point is that these anti-amyloid agents, there's several of them, we have to learn how to use them, and importantly, we have to understand the risks versus the benefits. And we should definitely talk a little bit about side effects and adverse events.

Dr. Agronin:
Sure, this is really important, as more people are having access to these either through clinical trials or now that we have one on the market. There's talk about side effects.

We focus on something called ARIA. It stands for amyloid-related imaging abnormalities. And what this refers to is the fact that often, we don't know that there's a side effect until we actually do an MRI and we see essentially 2 types of white matter lesions that can emerge during treatment. One of them we call ARIA-E, which refers to edema, or vasogenic edema, which is believed to be a result of amyloid

being pulled out of small vessels and you get a little leakiness. And so you may see a spot or spots of edema that appear.

The second is called ARIA-H, which stands for microhemorrhages or hemosiderosis, basically, teeny little areas where you get a little bleeding and then you get the resorption of that over time. These are usually asymptomatic. When we do see symptoms, people can report headache, dizziness, or confusion. Often we don't even know about them until we see it on the MRI. And we do know that individuals with a particular genetic profile, the APOE ε4, especially if they're homozygous, do tend to have a higher risk of this. And they typically resolve over time.

So even though it can sound pretty daunting that someone has edema in the brain, we have to realize that often it's asymptomatic, it does get better, but these are notable risks that we need to factor into our conversation.

So, you know, essentially, Dr. Isaacson, you outlined these. Where do you think the field is heading in the next couple of years?

Dr. Isaacson:
Well, I think some of these treatments, for example, solanezumab, which we didn't mention, is actually being studied in people before they have symptoms or at the very earliest stage, the mildest stage or preclinical or pre-symptomatic or just early symptomatic Alzheimer's disease. Just starting these anti-amyloid agents before symptoms, is that's what's necessary to not just slow decline by 15%, 20%, 30%? Or does that mean we need to start earlier so that we can actually show symptomatic improvement? I think what we need to do is start earlier. I think we need to type the patients better, meaning maybe they have amyloid and just a little bit of tau, versus if people have amyloid and a lot of tau. Anti-amyloid agents may work differently in those in those patients. So whether we stage them in terms of their cognitive status or we stage them in terms of their biological signature, these anti-amyloid and other anti-tau and other anti-neuroinflammation, drugs, etcetera, we need to really tease out exactly when to deploy them at what dose and in what person to have the most benefit.

Dr. Agronin:
Those are really good points. So this has been a brief but great discussion. Unfortunately, our time is up. To everyone, thanks for listening.

Announcer:
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