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Released: 07/25/2024
Valid until: 07/25/2025
Time needed to complete: 1h 03m

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Breaking Ground: The Latest Data on AD Disease-Modifying Therapies

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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Dr. Hardy:
This is CME on ReachMD and I'm Dr. John Hardy. Today, we're going to discuss what disease-modifying therapies are currently available to treat Alzheimer's disease. For those of you are interested, I recommend this review from Karen and De Strooper, which came out the year before any of the positive reports. And the reason I like this is because it forecasts what was needed for a successful anti-amyloid drug. In this theoretical slide it shows an anti-amyloid antibody being given at the start there, on the top left. It removes amyloid from the brain, and the dropping line shows that. And it's only when the amyloid removal has happened that you see the red line of the clinical symptoms diverging from the dotted red line of the placebo. So, this forecast which anti-amyloid therapies would work, and it's a very astute review, and I really recommend that people who are interested read this review and have a look at it.

What DMT's am I going to talk about? Well, briefly, I'm going to talk about aducanumab. This was the first one which was approved, but it's been withdrawn. Its approval was controversial. There were two trials, one of which gave positive results, and one of which gave ambiguous results. And so, there was a lot of discussion. It was approved, but now it's been withdrawn from sail.

The second is lecanemab, LEQEMBI, which I'm going to show you the data from, that has been approved and is now available in the States and in other locations, too. Then, the third I'm going to briefly talk about is donanemab, which is still in the approval process. And then finally, I'm going to talk very briefly about gantenerumab, which failed in the clinical trial, but it's being reformulated. The reason I'm going to talk about that is, it illustrates a failure and why, can see immediately, based on the review, why it failed.

So, these are the amyloid characteristics of those drugs. Let's start with LEQIMBI, lecanemab, in red. You can see that removed amyloid effectively, and that's obviously now approved. Donanemab also removes amyloid from the brain. That's still in the approval process. And aducanumab is the one that I mentioned where it was approved, but the approval was controversial because its effects were too marginal to convince all the reviewers. And then, really interestingly, there's gantenerumab, which was published about 18 months ago, and that, you can see why it failed its clinical endpoints. It simply did not remove enough amyloid in the time it was given.

Let's have a look at the lecanemab data. Here you see lecanemab removal by amyloid very clearly. By 12 months, you've nearly got rid of all of the amyloid out of the brain. It sucks amyloid out of the brain. Here are the clinical symptoms in the same study, showing clear divergence from the placebo control. Important to notice, it clearly slows the disease, but it doesn't stop the disease, and that is also an important thing that we have to consider.

Why did previous anti-amyloid therapies not work? Well, a major reason that previous anti-amyloid therapies did not work is because they stopped amyloid buildup, but they did not cause amyloid removal from the brain. So, if the brain was already full of amyloid, these drugs were basically given too late. Another subsidiary reason is that the diagnostic accuracy in many of the earlier clinical trials in

which anti amyloid therapies were given was very poor, something of the order of 70%. That isn't true of the most recent cases, but it was true of the earlier trials. A major issue in all of these trials, in all of these anti-amyloid trials, is the complication in the trials of amyloid-related imaging abnormality, which you will also have to think about when you give anti-amyloid therapies.

So, thanks for listening to this lecture.

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