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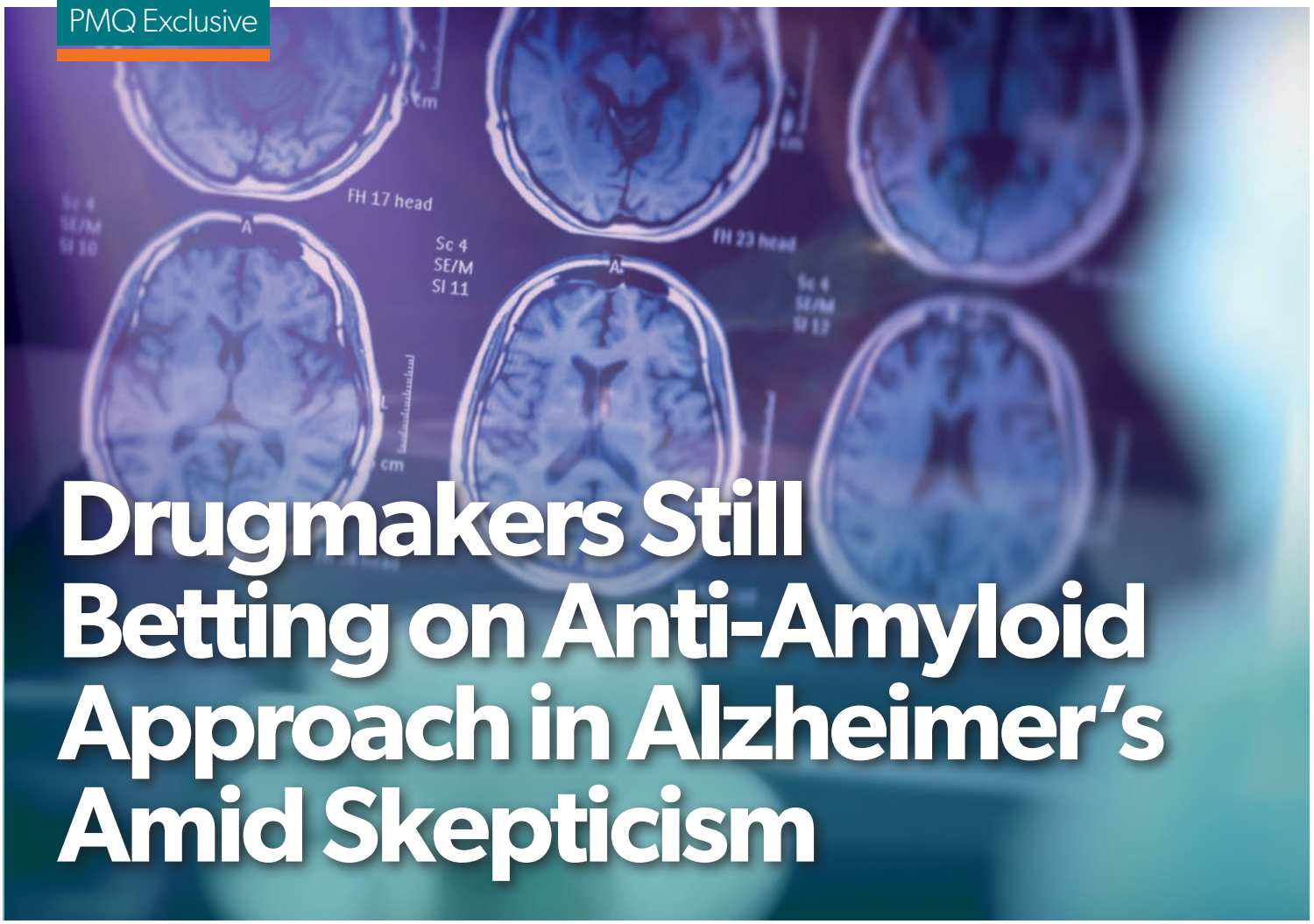


Drugmakers Still Betting on Anti-Amyloid Approach in Alzheimer's Amid Skepticism

Companies are pushing ahead with anti-amyloid drugs despite setbacks over the years and calls to move beyond amyloid and look at other biomarkers.

By Jessica Kim Cohen

AFTER DECADES of anti-amyloid drugs failing to improve Alzheimer's disease symptoms and amid debate regarding whether researchers and pharmaceutical companies should abandon the strategy altogether, the US Food and Drug Administration has in the last two years controversially approved two new treatments that clear the hallmark signs of this memory-robbing illness.

The FDA kicked off the new year by approving Leqembi (lecanemab), Biogen and Eisai's much-anticipated drug that treats Alzheimer's disease by attacking beta-amyloid clusters in the brain. Leqembi follows the agency's approval in June 2021 of Biogen and Eisai's Aduhelm (aducanumab) as the first drug that clears beta-amyloid.

Since the 1990s, the "amyloid hypothesis" has been the dominant theory of what causes Alzheimer's. The theory holds that the accumulation of the sticky beta-amyloid protein in the brain hinders cellular communication, causing a cascade of other issues, such as the abnormal formation and build-up of the protein tau and neuroinflammation that kill brain cells. The discovery that patients with Down syndrome or early-onset Alzheimer's due to abnormalities in the APP gene tend to have clumps of beta-amyloid in their brains has lent further support to this hypothesis, but not everyone agrees that beta-amyloid is Alzheimer's root cause and in recent years, more researchers have challenged the dogma.

In the case of Aduhelm, 10 out of 11 experts on an independent committee charged with advising the FDA remained unconvinced after reviewing the available evidence that lowering beta-amyloid improved Alzheimer's patients' symptoms. Aduhelm had shown mixed results in Phase III trials, with only one of two studies successfully meeting a primary endpoint of slowing cognitive decline. The FDA went

against the expert committee's advice and approved Aduhelm on the basis that both studies consistently reduced amyloid plaque in the brain, which the agency said was expected to result in clinical benefits.

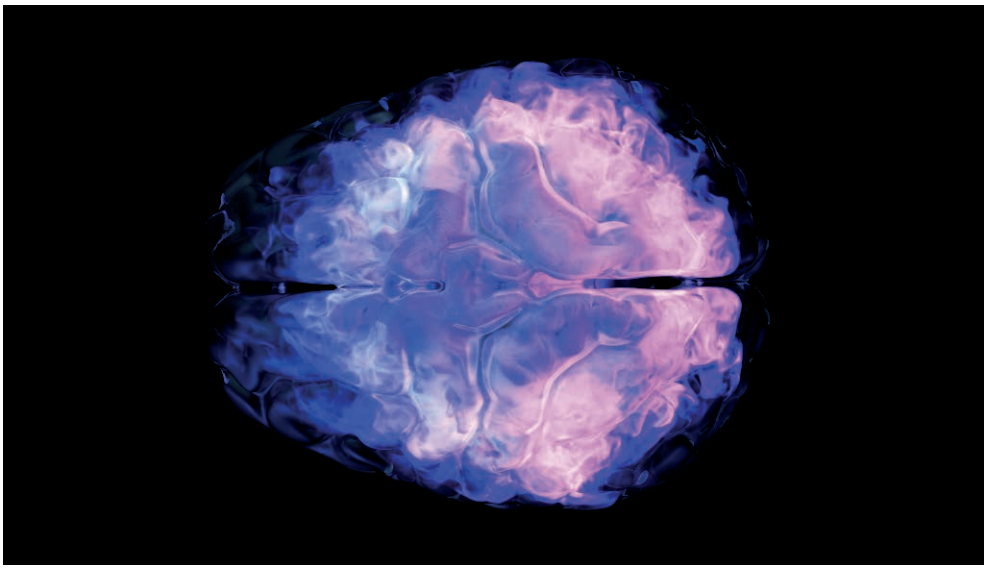
Many Alzheimer's experts decried the agency's decision to grant Aduhelm accelerated approval. Prominent institutions decided not to offer the treatment, reasoning that its questionable benefits aren't worth the risk of the brain swelling and bleeding it can cause. They were further deterred by its initial yearly price of $56,000, which Biogen later slashed in half. The US Centers for Medicare & Medicaid Services limited coverage of the drug and possible other, future monoclonal antibody treatments targeting amyloid for Alzheimer's, pending further evidence of clinical benefits. Legislators launched an investigation into the FDA's regulatory process for approving the drug and concluded in December that the process was "rife with irregularities."

Biogen in a statement issued in response to the congressional investigation said that the company stands by the integrity of its actions. "Alzheimer's is a highly complex disease and we have learned from the development and launch of Aduhelm," the company said. "That process is continuing to inform our work as Biogen introduces new innovative treatments to the market."

Given this history, there was much interest in how the agency would view the data on Leqembi. Like Aduhelm, FDA granted Leqembi accelerated approval based on its ability to clear amyloid, but unlike the former, the latter slowed cognitive decline in patients experiencing early Alzheimer's symptoms in a Phase III trial. At 18 months, patients on Leqembi averaged a score of 1.21 on the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB), compared to an average score of 1.66 for those on placebo. The 0.45 difference in scores between the two groups translates to a 27 percent slower rate of cognitive decline for Leqembi-treated patients, Biogen and Eisai reported.

In a statement after Leqembi's approval, Biogen President and CEO Christopher Viehbacher described FDA's regulatory decision as "recognition of the many scientists and doctors who have, over many years, patiently and persistently worked to find a treatment for this highly complex disease."

While supporters of the beta-amyloid theory may be celebrating Biogen and Eisai's win, questions remain as to whether the drug's modest slowing of cognitive decline will actually prove useful for patients and if payors will reimburse the therapy, even though Eisai priced Leqembi at $26,500 – less than the cost of Aduhelm. Moreover, experts in the field continue to debate whether the FDA was right to give further credence to the beta-amyloid theory in Alzheimer's disease at a time when pharmaceutical companies like Roche and Eli Lilly continue to experience disappointment with their anti-amyloid drug development programs.



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By granting accelerated approval to Aduhelm, the FDA established a path to market for drugs that can clear amyloid as a predictor of slowing cognitive decline in Alzheimer's patients, said Jonathan Jackson, a cognitive neuroscientist and the executive director of the Community Access, Recruitment, and Engagement Research Center at Massachusetts General Hospital and Harvard Medical School.

That's given pharmaceutical companies, some of which launched anti-amyloid drug trials more than a decade ago, hope that their therapies can be approved, too, if the agents reduce beta-amyloid. "Anti-amyloid therapies are enough, right now, to meet the FDA's criteria" for approval, Jackson said.

Optimism despite failure

The history of anti-amyloid drugs is rife with failure. Roche shouldered negative news on two of its anti-amyloid drugs last year. In November, Roche's gantenerumab failed to slow cognitive decline in patients with early Alzheimer's in a Phase III trial. A few months earlier, crenezumab also didn't prevent cognitive decline in a study of pre-symptomatic patients with a mutation in the PSEN1 gene that causes early-onset Alzheimer's. Earlier this month, Lilly said it would no longer develop solanezumab, designed to target soluble amyloid beta, after it failed to remove plaque or hinder amyloid accumulation in patients in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease Study..

Perhaps because the story of Alzheimer's drug development has been so bleak, researchers and pharmaceutical companies are eager to bask in the few bright spots that have emerged recently in the anti-amyloid space. For example, a Phase III trial comparing Lilly's donanemab against Aduhelm in early Alzheimer's patients showed that 37.9 percent of patients on donanemab achieved brain amyloid clearance after six months, compared to 1.6 percent of patients treated with Aduhelm.

In a separate Phase II trial comparing donanemab and placebo, early Alzheimer's patients on Lilly's drug had better composite cognition scores and ability to perform daily activities. But when Lilly submitted this data to the FDA in January seeking accelerated approval, the agency rejected it, saying the drugmaker didn't have enough data from patients who had been taking donanemab for at least 12 months. Lilly has said it will seek traditional FDA approval for donanemab in mid-2023 based on data from an ongoing Phase III confirmatory trial evaluating the safety and efficacy of the drug in patients with early symptomatic Alzheimer's

and the presence of tau pathology. The company is primarily interested in how patients on donanemab do on the integrated Alzheimer's Disease Rating Scale, which measures cognitive abilities and daily activities, and is also tracking changes from baseline in amyloid and tau levels as secondary endpoints.

Before drawing conclusions about the validity of the amyloid hypothesis, it's important to remember that all these anti-amyloid drugs work in different ways and target different points of the amyloid pathway, said Ronald Petersen, director of Mayo Clinic's Alzheimer's Disease Research Center. As such, the failure of one drug shouldn't necessarily endanger the potential of others, he noted.

"If there is a common thread among all of these, it's that the ones that seem to be clinically beneficial do show evidence of lowering amyloid plaque levels in the brain," Petersen said. Roche's gantenerumab trial, for example, didn't reduce amyloid as much as expected, which according to some experts, supports the hypothesis that clearing amyloid is associated with clinical outcomes, even if the drug itself wasn't successful.

There's promise behind anti-amyloid treatments, said Gwenn Garden, co-director of the Duke University-University of North Carolina Alzheimer's Disease Research Center. Recent setbacks haven't changed her stance on that, she said, and if anything, drugmakers seem more optimistic about anti-amyloid treatments than in years prior.

"The companies that are running [anti-amyloid drug] trials now are already invested in this, and have been for many years," Petersen added.

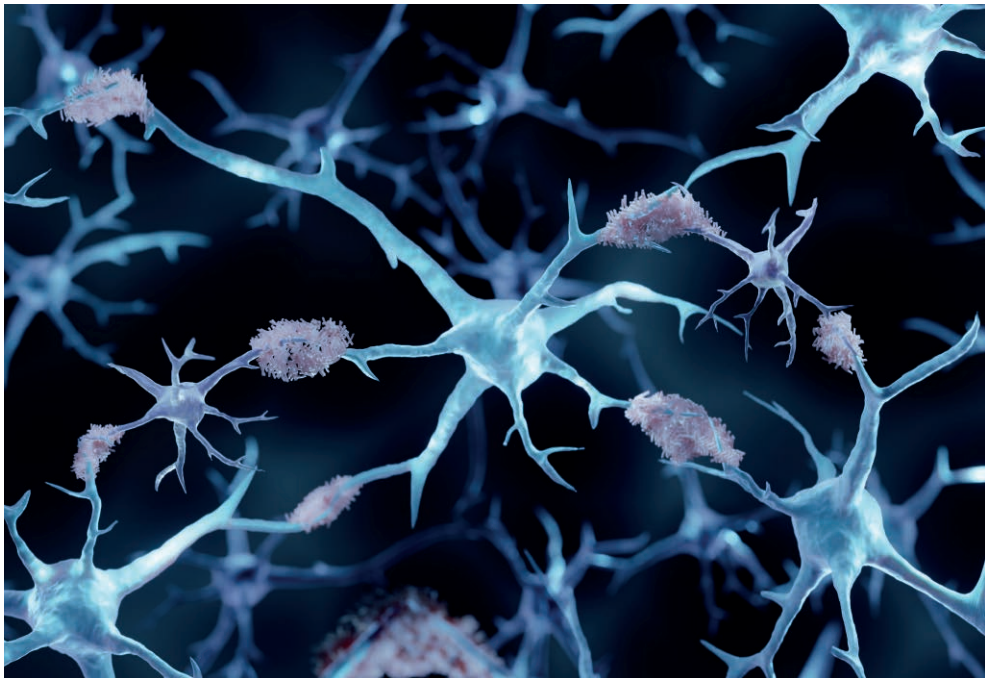
Still, drugmakers' future investments into developing and commercializing these types of drugs may be swayed by payors' decisions, particularly in light of the difficult reimbursement landscape. Many insurers, including Medicare, have restricted coverage of Aduhelm and similar therapies. After CMS decided to only cover Aduhelm for patients in clinical trials, Biogen significantly scaled back marketing and commercialization plans for it. CMS last month said it would not reconsider its coverage policy for anti-amyloid Alzheimer's drugs like Aduhelm and Leqembi yet, but pledged to "expeditiously review any new evidence that becomes available that could lead to a reconsideration."

Commercial efforts for Leqembi will be "scaled appropriately in accordance with patient access to Leqembi via all payor channels and traditional approval by the FDA," an Eisai spokesperson wrote in an email. The clinical meaningfulness of Leqembi is supported by the Phase III trial results, including the 27 percent slower rate of cognitive decline and 31 percent lower risk of patients converting to the next stage of Alzheimer's disease compared to placebo, as well as the drug's effect on amyloid, tau, and neurodegeneration biomarkers, he added.

Even though some researchers and drugmakers aren't giving up on the amyloid hypothesis, there are plenty of skeptics. According to Robert Friedland, a professor of neurology at the University of Louisville School of Medicine, the amyloid hypothesis is incomplete. It doesn't fully explain the causal link between amyloid and Alzheimer's, and he noted that there are people without cognitive impairment who have amyloid deposits in the brain.

Moreover, in the trial that led to Leqembi's approval, patients on the drug scored, on average, less than half a point better than patients on placebo on the 18-point CDR-SB scale. While the finding is statistically significant, it represents a modest change that may not translate to noticeable improvements in patients' memory and other functions, according to Friedland.

Despite many anti-amyloid therapies before Leqembi failing to show any clinical efficacy, in the wake of the Aduhelm approval, "it seems to me that [companies] are just more focused on this particular approach to the disease than ever," he noted.



All-in on amyloid

Indeed, pharmaceutical companies say they're continuing to move forward with anti-amyloid trials.

Roche, which has shuttered many of its gantenerumab and crenezumab trials, is continuing to develop other Alzheimer's therapies, including those that target amyloid, tau, and neuroinflammation. That includes a formulation of gantenerumab called trontinemab, which uses a different technique to try to increase the therapy's ability to reach the brain and is in a Phase Ib/IIa trial.

"We will be working with the Alzheimer's community to ensure the learnings from these studies are used to further the scientific debate in this area of high unmet need," a Roche spokesperson wrote in an email regarding recent lackluster results on gantenerumab and crenezumab. "With every negative study, we and the scientific community learn."

John Sims, Lilly's global brand development leader and senior medical director of neurodegeneration, said he's confident in the potential of anti-amyloid drugs to treat Alzheimer's. He maintains that a correlation between amyloid and clinical outcomes has been seen in studies of Leqembi and donanemab, as well as in gantenerumab's trials. Much of the challenge, in his view, has been deciding on the right dose and whether to give patients treatments at an earlier stage of disease.

Despite Lilly's recent decision to stop developing solanezumab, the drugmaker is moving forward with Phase III trials for its anti-amyloid drugs donanemab and remternetug. In a statement explaining its decision, Lilly said that since solanezumab only binds to soluble amyloid-

beta, the firm didn't expect it to significantly remove amyloid plaque deposits. But, donanemab and remternetug are different, Lilly noted, because they specifically target amyloid plaque deposits and appear to clear plaque in treated patients.

Eisai, meanwhile, has applied to convert Leqembi's accelerated approval into a traditional FDA approval, and Michael Irizarry, deputy chief clinical officer of Alzheimer's disease and brain health at the company, highlighted several studies that can provide additional insights into the drug's activity. In the AHEAD 3-45 trial, for example, Eisai is testing whether Leqembi can delay or prevent cognitive decline in patients who don't have Alzheimer's symptoms but have intermediate or elevated levels of amyloid in the brain.

As part of the Dominantly Inherited Alzheimer Network Trials Unit's Phase II/III Tau NexGen trial, a clinical research project led by Washington University School of Medicine in St. Louis, patients are being administered Leqembi and randomized to also receive either an investigational Eisai anti-tau therapy, E2814, or placebo. The trial involves patients with either a known genetic mutation that causes Alzheimer's or who have a dominantly inherited Alzheimer's disease mutation in their family.

Eisai is no longer involved in the development or commercialization of Aduhelm. Eisai and Biogen inked a collaboration deal in 2017 for Aduhelm, but the companies amended their financial agreement last year after Eisai decided to bow out of marketing the drug. Even though market analysts at one time believed Aduhelm had mega-blockbuster potential and could bring in $9 billion in peak sales, Biogen reported only $1 million in sales for the drug in the fourth quarter of 2021, the months after its FDA approval. In full-year 2022, Biogen reported Aduhelm sales of $4.8 million. There is no longer a commercial effort behind Aduhelm, Biogen's Viehbacher said during a call with investment analysts to discuss 2022 earnings results in February. A spokesperson confirmed via email that Aduhelm remains available to patients, but there are no active commercialization efforts.

"Our focus is on Leqembi – we believe that is the product that is most appropriate for patients," Viehbacher told analysts on the call. Biogen expects to see modest revenue from Leqembi this year, although commercialization expenses will likely exceed revenue.

"Leqembi is our absolute priority, and Aduhelm is not being actively commercialized anywhere," he added.

He pointed out that, when compared to placebo in a Phase III trial, Leqembi slowed decline of activities related to daily living by 37 percent. Eisai, which is leading development efforts for Leqembi, has filed for regulatory approval in the EU and Japan and is developing a subcutaneous formulation and an indication for maintenance dosing, he added.

"In the short-term, the launch in the US is really going to be constricted until we get to reimbursement," Viehbacher said. "That's expected to occur once we have traditional approval." Biogen and Eisai still have a co-commercialization pact on Leqembi, and Eisai is leading discussions with CMS. Viehbacher noted lawmakers and groups like the American Academy of Neurology have written letters to CMS in support of covering Leqembi.

Beyond amyloid

Mass General's Jackson, a self-described "amyloid skeptic," said the industry needs to look at other biomarkers beyond amyloid. He expressed concern that while anti-amyloid drugs may succeed in slowing cognitive decline somewhat, this might not be enough to actually improve the quality of life for patients who are already experiencing Alzheimer's symptoms.

"I do worry that in order to have a meaningful difference in the daily lives of people, we're going to have to look beyond anti-amyloid therapies," Jackson said. "It may not necessarily be the transformational change that millions of families have been waiting for."

Anti-amyloid drugs could prove useful for prevention, he mused, for patients with biomarkers indicating disease development, and he's interested in seeing results of studies on pre-symptomatic patients. But he suspects patients who are already experiencing cognitive decline will likely need a combination of therapies, such as anti-amyloid and anti-tau therapies and drugs that reduce inflammation in the brain.

"There will be enough hope, enough demand, enough innovation and investment in the coming years to dramatically improve on what we're seeing here," he added.

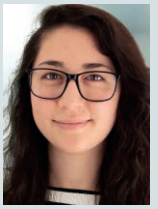
For example, there are a growing number of ways to monitor tau, a protein whose presence in neurons some studies suggest more closely correlate with symptoms of cognitive decline. Pharmaceutical companies are pursuing therapies that target tau, though these are in earlier development stages than anti-amyloid therapies.

Biogen late last year initiated a Phase II trial for an anti-tau medication, BIIB080, in which participants must show evidence of amyloid accumulation through either a PET scan or a cerebrospinal fluid sample to be eligible, and it has another anti-tau therapy, BIIB113, in a Phase I trial. Lilly, meanwhile, is studying an OGA enzyme-inhibiting anti-tau therapy in a Phase II trial, in which it will measure how the drug impacts brain tau deposits in PET scans as a secondary endpoint.

Roche has two anti-tau therapies in trials: bepranemab, in a Phase II trial for patients with early Alzheimer's, and semorinemab, in an ongoing Phase II open-label extension study for patients with mild to moderate Alzheimer's. Roche is using PET scans to measure tau burden in the brain as a secondary outcome measure in its bepranemab trial, and to participate in the study, participants must also demonstrate evidence of amyloid accumulation.

In addition to studying the anti-tau therapy E2814, Eisai is conducting early trials of drugs targeting neurodegeneration by trying to preserve synapses, Eisai's Irizarry said. "All of these processes are active in Alzheimer's disease," he said. "We think that a range of targets will be required to tackle Alzheimer's disease and to have the right cocktail of treatments for the appropriate patients."

Mayo's Petersen, meanwhile, is of the view that the modest effect on patients' outcomes seen in recent anti-amyloid trials is still clinically meaningful. He further noted that the field shouldn't expect amyloid-lowering drugs to dramatically improve clinical outcomes, especially when they are given to symptomatic patients with memory problems and other cognitive impairment. But like others, Peterson is also hopeful that compared to past single-agent approaches, strategies involving combination treatments targeting amyloid or other proteins detected in a patient's brain might have a better shot at improving Alzheimer's symptoms. "I don't think we should expect a cure for Alzheimer's disease in the near future," Petersen said, but he predicted that after this period of testing out largely monotherapy approaches, the era of combination therapy is next in Alzheimer's. PMQ



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