
Those multisyllable drug names may not trip off the tongue of even the most articulate, but they’re all treatments developed to slow down a disease that eventually robs people of the simplest of words.

With varying degrees of success, these monoclonal antibodies, or mAbS for short, bind to and remove a protein from the brain called amyloid-β, a hallmark of Alzheimer disease (AD). Researchers have focused on amyloid-β for 3 decades, ever since 2 UK scientists proposed that deposition of the protein in the brain was “the central event in the aetiology of Alzheimer’s disease”—what has come to be known as the amyloid cascade hypothesis. Although these mAbs clear amyloid-β, for the most part they have failed to slow the progression of cognitive decline in people with AD.

In July, however, lecanemab (marketed as Leqembi) became the first anti–amyloid-β mAb ever to receive traditional approval from the US Food and Drug Administration (FDA). Earlier this year, the FDA had granted lecanemab accelerated approval. That regulatory pathway is reserved for drugs to treat serious conditions for which there is an unmet medical need. Such drugs must affect a surrogate end point—in this case brain amyloid levels—that is “reasonably likely” to benefit patients clinically.

Lecanemab earned traditional approval—winning it broader Medicare coverage—because a confirmatory study required as a condition of accelerated approval verified its clinical benefit, according to the FDA.

Less than 2 weeks after lecanemab’s traditional approval, researchers reported in JAMA that donanemab significantly slowed clinical progression in patients with early Alzheimer disease after nearly 18 months of follow-up, and manufacturer Eli Lilly announced it had filed for traditional approval of the drug and expected a decision from the FDA by year’s end.

Medicare is expected to pay for the bulk of treatment with anti–amyloid-β mAbs in the US. For drugs in that class that receive accelerated approval, the agency will cover costs only for beneficiaries in randomized trials. Traditional approval means Medicare will pay for treatment outside clinical trials as long as clinicians submit information about their patients to a registry designed to collect information about real-world use.

Still, lecanemab treatment is expensive, with an annual wholesale acquisition cost of $26,500 for average-weight patients for the drug alone; for some patients, drug co-pays could amount to roughly $14.50 per day. It’s also cumbersome, requiring every-other-week infusions plus multiple magnetic resonance imaging (MRI) scans, and carries the risk of a life-threatening event. And it’s far from a cure, with some skeptics questioning whether patients and their families will notice any treatment benefit. All these factors could limit its uptake.

Proof of the Amyloid Hypothesis?
Before lecanemab, aducanumab was granted accelerated approval in June 2021. The two drugs are considered to be the first FDA-approved disease-modifying therapies for AD, unlike treatments that address symptoms but not the underlying cause.

But not so fast, says Russell Swerdlow, MD, director of the University of Kansas Alzheimer Disease Research Center.

“My view is we need to be cautious about what we think of as disease modifying,” Swerdlow, whose research focuses on brain bioenergetic changes, noted in an interview. “To say the monoclonal antibodies are disease modifying because they remove plaques is primarily true if the plaques are causing the disease. What if the plaques are not primarily responsible for the disease?”

Perhaps the plaques induce inflammation “and that turns people’s cognitive performance down a notch,” he explained. Patients might get a bit of a boost from clearing plaque, “but the disease is still progressing,” Swerdlow said. “You’ve affected the biology, but until we truly fully understand how the disease starts...and what’s
really going wrong, we don’t know what’s disease modifying or not.”

University of Texas at San Antonio neuroscientist George Perry, PhD, echoed Swerdlow’s comments. “Amyloid plays a critical role in the pathway of Alzheimer disease, but that doesn’t mean it’s a cause,” Perry, whose research focuses on how brain cells respond to oxidative damage, said in an interview. “We don’t even know how amyloid gets deposited in the brain.”

And yet, he said, believers in the amyloid hypothesis “predicted that getting rid of the amyloid was like going to Lourdes,” the major Catholic pilgrimage site where spring waters are purported to have healing properties.

Most anti–amyloid-β mAbs, though, haven’t even made it as far as an FDA rejection.

Crenazeumab didn’t reduce clinical decline in phase 3 trial participants with early AD, researchers reported in JAMA Neurology in September 2022. Two months later, Roche confirmed that it planned to shut down all clinical trials of gantenerumab in early AD because the drug had repeatedly failed to demonstrate a significant clinical benefit. And in March of this year, Eli Lilly announced that it was ending clinical development of solanezumab after a trial found it failed to slow cognitive decline in individuals who at baseline were cognitively normal but had elevated brain amyloid levels on positron emission tomographic (PET) scans. (In a previous trial, the drug did not slow cognitive decline in people with mild AD.)

Aducanumab was the first new AD treatment in 18 years, but in granting it accelerated approval, the FDA bucked its own panel of outside advisors, none of whom voted “yes” when asked whether the treatment was effective against Alzheimer disease. Aducanumab cleared amyloid-β, but clinical trial findings were mixed as to whether it slowed cognitive decline.

Some medical centers, citing the need for more evidence about aducanumab’s efficacy, immediately decided not to use the drug. Then Medicare said it would cover the expensive treatment only for patients participating in randomized trials. The same would be true for any other anti–amyloid-β monoclonal antibody that received accelerated and not traditional approval.

Meanwhile, “Aduhelm remains available to patients, but there are no active commercialization efforts behind the product,” Allison Parks, a spokeswoman for Biogen, which developed the drug with Eisai, said in an email to JAMA. Parks declined to say how many patients have been treated with aducanumab since its accelerated approval.

Who Might Benefit, Who Might Not?

Mayo Clinic neurologist David Knopman, MD, was one of 3 members of the FDA advisory committee that reviewed aducanumab who resigned after the agency approved it. (He had recused himself from that particular meeting because he had served as site principal investigator for a trial of the drug.)

Knopman and his colleagues are preparing to administer lecanemab, but he’s not sure how much patients stand to gain from it.

In a phase 3 trial, “it delayed progression at 18 months by about 5 months,” Knopman noted in an interview. “Is that clinically meaningful? I don’t know. What really counts is where you are at 36 months. Is it still a 5-month delay? That’s trivial.” On the other hand, he said, if the difference between treated patients and untreated patients continues to increase as time passes, “it’s a win.”

Questions about long-term clinical benefit aren’t the only ones that make him anxious. Knopman said. Post hoc subgroup analyses of clinical trial data, reported in a supplement, found that lecanemab didn’t seem to benefit much patients younger than 65 years or women, he explained.

Women are twice as likely as men to develop Alzheimer disease, and the authors of a recent Viewpoint in JAMA Neurology expressed disappointment that phase 3 trials of lecanemab and aducanumab did not expand sex-disaggregated analyses in the main reporting of results. The supplement for the lecanemab trial publication “revealed noteworthy sex differences,” the Viewpoint authors wrote. Although the trial found that, overall, lecanemab delayed progression by 27%, the difference between the treated and placebo groups was 43% in men and only 12% in women. Similar discrepancies were seen in the aducanumab trials, the Viewpoint authors pointed out.

A letter to the editor of the New England Journal of Medicine, echoing the Viewpoint, noted that patient sex seemed to be relevant to the lecanemab trial’s clinical significance at the individual level. In response to the letter, 3 trial investigators wrote that “a treatment effect across all end points was observed among women as well as among men, although the effect was numerically smaller among women.” However, they noted, “the trial was not powered to evaluate individual subgroups.”

The 27% average difference between the lecanemab and placebo groups is just that, an average, Donna Wilcock, PhD, MS, a professor of AD research at the Indiana University School of Medicine who wasn’t involved in the trial, said in an interview. “I think what we’ve failed to think about is that is the average for everyone who participated in the trial,” she explained. “It makes it a little frustrating when people say that’s going to be the outcome for every patient.”

Some patients benefited much more than average, while others gained little, she noted. “Probably a reasonable number of people out there stand to have their quality of life extended beyond belief from this drug,” Wilcock explained. On the other hand, she pointed out, because of adverse events related to the drug, some treated patients might decline more quickly than they would have if they hadn’t received it.

“Unfortunately, in the trials, once you try and break your group down to those subgroup analyses, you lose all your power,” Wilcock said. “The next leap will be how do we identify those who will truly benefit?”

Still, the trial results suggest that lecanemab’s benefit in clinical trial participants was so minimal that most treated patients and their caregivers might not even notice a difference, Ohio State neurologist James Burke, MD, and coauthors wrote in a recent article. “Before adopting lecanemab, we need to know that lecanemab isn’t less effective, vastly more harmful, and 100 [times] more costly than donepezil.” Donepezil, approved in 1996, is an acetylcholinesterase inhibitor sold as a pill called Aricept, among other names, and as a patch called Adlarity.

In an interview, Burke expressed skepticism that any of the outstanding questions about lecanemab’s efficacy will ever
be answered without a large trial lasting at least 5 years. With information collected by registries, he said, “I think we can learn a lot about the safety question. I think we will learn nothing about the efficacy question.”

If lecanemab appears to slow the decline of Alzheimer disease in the real world, “maybe providers selected people for treatment who were likely to do better, people who have the capacity to come for a visit every 2 weeks,” he said. “We’re not going to learn anything…without randomization.”

The Centers for Medicare & Medicaid Services (CMS) has set up the Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease Registry and is also working with other organizations preparing to open their own registries. The Alzheimer’s Association launched the Alzheimer Network for Treatment and Diagnostics (ALZ-NET) registry last year; ALZ-NET is paying participating medical practices for their time, according to the registry’s frequently asked questions.

On July 27, a group of public health researchers and health policy experts, including Perry, sent a letter to Xavier Becerra, JD, secretary of the US Department of Health and Human Services, and CMS Administrator Chiquita Brooks-Adams, expressing concern that “Leqembi registries developed by medical societies, medical centers, nonprofit organizations, or other non-governmental entities may limit access to their respective population-level data, potentially making it difficult for CMS and other researchers to conduct independent analysis of the data.”

ARIA—a Sour Note
In a 2002 article, researchers reported seeing cerebral microhemorrhages in a mouse model of Alzheimer disease after treatment with anti-amyloid-β mAbs.

These microhemorrhages came to be known as a type of brain change called amyloid-related imaging abnormalities (ARIA), potentially fatal complications of amyloid-clearing treatments such as lecanemab.

In the lecanemab phase 3 trial, symptomatic ARIA occurred in 29 of 898, or 3%, of patients treated with the drug. Serious symptoms associated with ARIA were reported in 6 of those patients. Clinical symptoms eventually resolved in 23 of the 29.

The FDA viewed the ARIA risk as serious enough to warrant a boxed warning for the entire class of anti-amyloid-β mAbs, including lecanemab. “ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events rarely can occur,” according to the boxed warning. “Serious intracerebral hemorrhages, some of which have been fatal, have been observed in patients treated with this class of medications.”

Before initiating treatment, clinicians should obtain a baseline MRI and then obtain more imaging prior to the 5th, 7th, and 14th infusions, according to the lecanemab label. If an MRI detects severe ARIA, even if it is asymptomatic, treatment should be suspended. The therapy should also stop if symptoms are moderate or severe, no matter the severity on the MRI.

Patients with mild ARIA on MRI who are asymptomatic or have mild symptoms may continue treatment.

One challenge related to ARIA is that symptoms differ, depending on where it occurs in the brain, Wilcock, who has a National Institutes of Health (NIH) grant to study the mechanism of ARIA in mouse models, pointed out. For example, she said, ARIA in the frontal lobe may increase confusion, while ARIA in the occipital lobe will affect vision. “It’s kind of like stroke—not everyone who has a stroke has the same disability.”

Some clinical trial participants stopped treatment because of significant ARIA symptoms, Madhav Thambisetty, MD, of the National Institute on Aging (NIA) noted in an interview.

It’s likely that ARIA will be more common in patients treated with lecanemab in the real world, because they will be more likely to have comorbidities that increase their risk, predicted Thambisetty, senior investigator and chief of the NIA’s Clinical and Translational Neuroscience Section Laboratory of Behavioral Neurosciences.

In the phase 3 trial, 6 patients died in the treatment group, and 7 died in the placebo group. “No deaths were considered by the investigators to be related to lecanemab or occurred with ARIA,” according to a published report of the results.

However, shortly after those results were published, researchers who weren’t involved in the clinical trial reported the case of a 65-year-old participant who died of multiple cerebral hemorrhages after receiving at least 3 lecanemab infusions, the most recent 4 days before receiving tissue plasminogen activator (tPA) for a stroke. “The extensive number and variation in sizes of the cerebral hemorrhages in this patient would be unusual as a complication of tPA solely related to cerebrovascular amyloid,” the authors noted. The case didn’t appear in the phase 3 trial report because the patient had received lecanemab during the open-label extension, 2 trial authors wrote in their response to the case report.

Thambisetty has been widely quoted about what he described to JAMA as a “glaring gap” in information about whether ARIA has lasting effects on cognition. “We still don’t know what happens to the cognition of these patients in the clinical trials,” he explained. “As a physician, I find that very concerning. We’re not going to be able to empower our patients to make data-driven decisions.”

Symptomatic ARIA might impact cognition more than asymptomatic ARIA, Thambisetty noted. However, he pointed out, Eisai and Biogen have lumped all ARIA cases in clinical trial participants together instead of stratifying them by severity.

As reported to the FDA and in the recent lecanemab phase 3 trial publication, “there was no adverse impact of ARIA on cognition or function (most ARIA was asymptomatic and resolved during the double blind phase),” Eisai spokeswoman Libby Holman told JAMA in an email. “Multiple analyses were performed to assess [the] impact of ARIA on cognition and function...”

But, Thambisetty countered, nothing has been reported specifically about the 2.8% of lecanemab-treated trial participants who experienced symptomatic ARIA (none in the placebo group did). “What were their clinical and cognitive outcomes at the end of the trial? Were they identical to those who were asymptomatic?” he asked. “If there was absolutely no association between serious ARIA and cognition, I think we would know by now.”

The APOE Conundrum
One of the great ironies of anti-amyloid-β mAbs is that patients who have 2 copies of the apolipoprotein E (APOE) ε4 gene are more likely to experience ARIA.
The ε4 allele is the strongest genetic risk factor for late-onset AD. Among White individuals, approximately 15% of those with AD but only about 2% of those with normal cognition carry 2 copies of the gene. Those who carry 2 copies, as did the trial participant who died after receiving lecanemab and tPA, have up to a 15-fold greater risk of the disease than individuals who carry 2 copies of the most common APOE allele, ε3, which doesn’t influence AD risk.

The lecanemab boxed warning about ARIA notes the relationship between AD and the APOE ε4 allele and recommends testing for APOE status before beginning treatment. The label states that before testing, “prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results.” Patients can still be treated without such testing, but they won’t know if they’re at a higher risk of ARIA.

APOE status isn’t routinely determined, Swerdlow noted. But, he pointed out, “based on the data from the monoclonal antibody trials, the individual’s APOE status helps inform the risk-to-benefit discussion.” A patient who carries 2 copies of the ε4 allele might have a more aggressive disease course than someone who doesn’t, Swerdlow said. That might spur more aggressive treatment, as with a mAb, but because of their increased ARIA risk, they might not have as clearcut a benefit, he pointed out.

In a recent Viewpoint that appeared in JAMA Neurology, Thambisetty and coauthor Robert Howard, MD, a University College London psychiatrist, noted that “a largely overlooked question has been the importance of APOE genotyping in clinical decision-making by physicians who are considering the drug for eligible patients with AD.”

They pointed out that participants in the lecanemab clinical trial who carried 2 copies of ε4 were more than 6 times as likely to experience symptomatic ARIA with edema or effusions and more than 3 times as likely to experience it with cerebral microhemorrhages.

At an event in December 2022, Ivan Cheung, then chair of Eisai’s US operations, advised that patients with 2 copies of ε4 should receive lecanemab only if they and their physicians agreed to close monitoring for brain bleeding, Thambisetty and Howard noted.

“I’ve had people go either way” when it comes to the prospect of determining their APOE status before initiating lecanemab therapy, Sam Grandy, MD, PhD, a professor of AD research at Mount Sinai in New York, said in an interview. One reason lecanemab candidates might not want APOE testing is because they worry that the information would somehow end up on their children’s medical records, he explained.

**Treatment Complexity**

Only a small percentage of people with early Alzheimer disease are likely to be eligible for lecanemab, a recent study coauthored by Knopman suggested.

He and his coauthors applied the clinical trial eligibility criteria for lecanemab and aducanumab to 237 people with early Alzheimer disease in the population-based Mayo Clinic Study of Aging. Based on the lecanemab phase 3 trial inclusion criteria, only 112 people in the study sample would be eligible for treatment; the trial’s exclusion criteria trimmed the number eligible down to 19, 8% of the original 237-person study sample. Even fewer, only about 5%, would have been eligible for aducanumab, according to the study. As Knopman and his coauthors noted in their article, **appropriate use recommendations** “have been created to help clinicians implement lecanemab treatment into real-world clinical practice and adhere closely to clinical trial inclusion and exclusion criteria.”

“Many conditions rendering patients ineligible are those we would expect in older adults, mainly for whom disease-modifying therapy (DMT) is developed,” the authors noted. “This is not a surprising conundrum.” They pointed out that others have suggested that many clinical trials for patients with chronic conditions exclude those who also have other conditions and are receiving other treatments.

The challenging logistics of providing and receiving treatment are another limitation in the clinic.

“It takes a multidisciplinary team to administer lecanemab,” Knopman noted. That team, he said, should include a behavioral neurologist who can distinguish mild cognitive impairment from depression, a neuropsychologist to interpret cognitive testing and make the correct diagnosis, a neuroradiologist to look for cerebral microbleeds at baseline, and a social worker to handle financial issues.

“Putting all these pieces in place takes some time,” he pointed out.

Although his practice attracts patients from throughout the upper Midwest, Knopman said, with lecanemab, “we will not treat people who live any farther than an hour and a half away.”

Sure, winter weather can make driving difficult in Minnesota, but that’s trivial compared with other reasons, he said. More importantly, in his view, is what might happen if a patient has a headache the day after receiving an infusion. Emergency medicine physicians at their local hospital might not be familiar with lecanemab, let alone the possibility that the headache could be a symptom of ARIA in patients treated with the drug. Even if local physicians do recognize this, they might not be able to schedule a brain scan immediately.

“It’s our view, and the view of many of our colleagues around the country who take safety seriously, that it needs to be done in our own center under our control, should an infusion reaction occur,” Knopman said.

At Indiana University, Wilcock said, “we’re doing a phased rollout.” The first phase will include patients who live in Indianapolis and surrounding areas, have been evaluated by a behavioral neurologist, and have undergone an MRI scan to make sure they don’t have evidence of microbleeds or a prior stroke and a PET scan or lumbar puncture to check that they have brain amyloid deposits. The next phase will involve patients who’ve been evaluated by neurologists not affiliated with the medical school. And finally, patients referred by their primary care physicians will be considered for lecanemab treatment.

The treatment complexity likely means that some candidates, especially those in traditionally marginalized populations, won’t be able to get lecanemab, Thambisetty pointed out. Patients need someone to accompany them to their every-other-week infusions and their MRI and PET scans and lumbar punctures. They might have family or friends who are willing to go with them but lack transportation or the ability to take time off work, Thambisetty said.

“This is much more complicated than simply going to an infusion center, getting hooked up, and then going home,” he explained.
Conflict of Interest Disclosures: Dr Gandy reported cofounding Recuerdo Pharmaceuticals; previously consulting for Johnson & Johnson, Diagenic, and Pfizer; currently consulting for Eisai, Cognito Therapeutics, GLG Group, SVB Securities, Guidepoint, Leerink, Third Bridge, MEDACORP, Atpep, and Vigil Neurosciences; previously receiving research support from Warner-Lambert, Pfizer, Baxter, and Avid; currently receiving research support from the NIH and the Cure Alzheimer’s Fund; and being a named inventor on a patent jointly assigned to Mount Sinai and the New York Stem Cell Foundation on the creation of human induced pluripotent stem cell–derived basal forebrain cholinergic neurons. Dr Knopman reported receiving no personal compensation for serving on data and safety monitoring boards for the Dominantly Inherited Alzheimer Network Treatment Unit study and for a Biogen α therapeutic; for being an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals, and the University of Southern California; and for serving as a consultant for Roche, Samus Therapeutics, Biovie, and Alzeca Bioscience. Dr Knopman reported attending an Eisai advisory board meeting for lecanemab in December 2022 for which he received no compensation. Dr Knopman reported having an unpaid consultation relationship with Biogen regarding secondary analyses of the double blind and open label lecanemab trials and receiving funding from the NIH. Dr Perry reported chairing the scientific advisory board for Synaptogenics and holding equity in the company and serving as a member of the scientific advisory board for Nervgen and editor-in-chief of the Journal of Alzheimer’s Disease. Dr Swerdlow reported receiving funding from the NIH and AstraZeneca; serving as a paid consultant for Nestle Health Science; holding a patent for “Bioenergetically Active Esters for Health and Disease;” and serving on the scientific advisory board of the BrightFocus Foundation and the Cogniket trial steering committee for Nestle Health Science. Dr Thambisetty reported no relevant financial conflicts of interest; being named the inventor on a patent application filed by the NIA for repurposing drug candidates for AD; serving on the FDA’s Peripheral and Central Nervous System and Psychopharmacologic Drugs advisory committees; and serving as vice chair of the McKnight Brain Research Foundation, for which he is not paid. Dr Wilcock reported having received research funding through competitive grant applications from the NIH and the Alzheimer’s Association and serving as editor-in-chief of Alzheimer’s & Dementia: The Journal of the Alzheimer’s Association. No other disclosures were reported.

Note: Source references are available through embedded hyperlinks in the article text online.