Are these pricey new Alzheimer's drugs worth it?

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Breakthrough new drugs that clear amyloid beta plaques from the brain

are shaking up the field of Alzheimer's disease research.

The fact that patients' mental deterioration slows when they're on anti-amyloid drugs is solid proof that abnormal amyloid proteins are one of the culprits behind Alzheimer's, essentially ending decades of debate over the so-called "amyloid hypothesis."

"We are confirming that amyloid truly is a component of the disease process, and when you address it, you see meaningful clinical benefit in individuals that sustained for some of these studies," said Rebecca Edelmayer, senior director of scientific engagement for the Alzheimer's Association.

But Alzheimer's experts warn that patients and their families should be wary of the hype surrounding drugs like Leqembi (lecanemab), Aduhelm (aducanumab) and donanemab (now in clinical trials).

They note that many patients won't be eligible to take the anti-amyloid drugs.

The drugs are now aimed at people in the early stages of Alzheimer's or dementia, and come with side effects that would bar their use in people taking blood thinners or with certain genetic risk factors.

Further, the drugs' limited ability to slow Alzheimer's progression might not be worth it given the continual transfusions, MRIs, PET scans and other tests that patients will have to undergo during treatment, the experts say.

"This is not a drug with no side effects, that would be cheap or easy to prescribe," Dr. Eric Widera, a professor of geriatrics at the University of California, San Francisco, said of donanemab, the latest drug to make a splash. "This is a very complicated drug that requires a tremendous

amount of monitoring, and our systems aren't even set up for that quite yet outside of these very specialized memory and aging centers."

In fact, worries that the expensive drugs will bankrupt Medicare are probably misguided given that so few Alzheimer's patients will be eligible for anti-amyloid treatment, said Dr. Ronald Petersen, director of the Mayo Clinic Alzheimer's Disease Research Center.

Much has been made of the $26,500 annual cost for Leqembi and $28,200 annual cost of Aduhelm.

Depending on how clinical criteria are applied, "somewhere between 8% and 18% of the population might be available for these drugs," Petersen said.

"It's far fewer than those who say, 'there are 6.7 million people with Alzheimer's disease in this country, it's going to bankrupt the world,'" he said. "Well, only a small subset of those people will be eligible for this. While it can be costly, I don't think it's going to be that dramatic."

Drugs making the latest headlines

July has seen some Earth-shaking developments in anti-amyloid treatment.

Earlier this month, Leqembi became the first Alzheimer's drug to receive full approval from the U.S. Food and Drug Administration, making it eligible for Medicare coverage.

And donanemab outperformed both Leqembi and Aduhelm in phase 3 clinical trial results presented in Amsterdam at the Alzheimer's Association International Conference this week.

All three drugs are monoclonal antibodies that attach to amyloid beta and help remove the problem protein from the brain.

"We saw that study participants at the earliest stage of disease had a greater benefit, with 60% slowing of decline compared to placebo," Edelmayer said of the donanemab trial. "I think nearly half, 47%, of the study participants at the early stages of the disease who received donanemab had no progression, no clinical progression at one year."

Those are folks who didn't progress to the next stage of disease, and, she said, that's significant. "That really means more time for them at an earlier stage of the disease process," Edelmayer added.

The donanemab trial results also appeared July 17 in the prestigious *Journal of the American Medical Association*, but a series of accompanying editorials raised lingering concerns about cost, access and safety risks associated with anti-amyloid drugs.

"Donanemab was very effective at eliminating its target, cerebral amyloid, but the clinical effect was comparatively weak," wrote Jennifer Manly and Kacie Deters, from the Taub Institute for Research on Alzheimer's Disease and the Aging Brain at Columbia University and the University of California, Los Angeles, respectively.

Even though amyloid plaques were cleared in 80% of the donanemab treatment group, disease progression was delayed by about four months during the 18-month trial, Manly and Deters noted.

"It looks like in the 18-month study, it slowed the decline by a quarter to a half a year in the whole population receiving donanemab," said Widera, co-author of another of the accompanying editorials. "That means that compared to the group that was getting placebo, you were doing better by a quarter to a half a year. You're still declining, but it just

doesn't look as fast."

Widera noted that on one Alzheimer's scale, donanemab slowed disease progression by about 3 points on a scale running from 0 to 144 points.

"There seems to be a benefit. It's doing something. It's just not doing it a whole lot, when you look at those absolute numbers," Widera said.

But Petersen argues that small numbers can equal huge clinical benefit. For example, he said, a person with a temperature of 98.6 is doing a lot better than one at 104—and that's on a scale that runs from 32 degrees freezing to 212 degrees boiling.

Plaques just one factor

Petersen pointed to another measure taken during the donanemab trial that covers six domains of dementia progression.

"One of the domains is memory, and if you read the descriptor of that scale, at 0.5, it says inconsistent forgetfulness causes some difficulties, benign forgetfulness," Petersen said. "If you go to 1.0, which is just one small change, it's now my forgetfulness is so significant, it's interfering with my daily activities. I can no longer do my activities because of my memory failure. Well, to me, that's a big deal, even though it's only a 0.5 change."

Still, the fact that drugs that so efficiently clear amyloid from the brain but aren't producing stronger benefits seems to demonstrate that Alzheimer's is being driven by more than just the plaques, Widera said.

"It does prove the amyloid hypothesis plays a role in cognitive decline because when you take away amyloid, people do better," he said. "It also in some ways disproves the idea that amyloid by itself is incredibly

important, because what you're seeing is despite being able to remove a tremendous amount of amyloid in the brain, you're only seeing a 3-point change on that entire 144-point scale."

Edelmayer agreed, noting that abnormal tau proteins and other factors also likely play a role in Alzheimer's.

"We need to continue to think about how we will be addressing the disease and attacking the disease from all angles," she said. "I think the field certainly recognizes that these antibody amyloid treatments are a first step in treating these diseases in the most effective manner possible, and it's likely that we're going to be seeing a combination approach of treatments."

Looking to the future, "you're going to be potentially seeing anti-amyloid treatments layered with other approaches that target tau biology, inflammation, the immune system, the blood vessels," Edelmayer said.

Not without complications

Many Alzheimer's patients won't be eligible for these drugs, and those who are eligible will have to go through some hassle to receive them.

"There will be a process for individuals before they can initiate treatment," Edelmayer said. "They'll need to be at the right stage of disease. They'll need to have confirmation of actually having Alzheimer's disease, with amyloid beta plaques in the brain. And they'll certainly have to have some baseline MRI imaging done because the treatments, as all treatments do, have side effects."

Removing amyloid from the brain increases the risk of a person suffering a brain bleed or cerebral edema, trials have shown. Baseline MRIs will help doctors track changes.

In the donanemab trial, about 24% of patients taking the drug suffered from cerebral edema compared to 2% of the placebo group, and 31% suffered a brain hemorrhage compared to 14%, one of the accompanying *JAMA* editorials noted.

Three people died in the donanemab trial due to drug-related brain bleeding and swelling, results show.

Because of this, Widera said, the drugs are not recommended for people who are taking blood thinners to lower their risk of a stroke or heart attack—and there are a lot of seniors taking such anticoagulants.

People also are at increased risk of brain bleed or cerebral edema if they are carriers of apolipoprotein E4 (APOE4), a genetic risk factor for Alzheimer's. The increased risk ran from 23% to 41% depending on the type of APOE4, compared with 16% for APOE4 noncarriers, editorialists noted.

"If people are homozygous APOE4 [meaning they inherited the marker from both parents], we're going to have very strong conversations with them about their increased risk of having side effects," Petersen said. "It doesn't mean we won't treat them, but we're going to have very, very frank conversations saying that there is a possibility here and that we're going to need to monitor you very closely."

Do risks outweigh benefits?

Alzheimer's patients also will need to be "generally healthy" to take these drugs, Petersen said.

"Poorly controlled diabetes, hypertension, cancer, those kinds of things may mitigate their eligibility for drugs," he said.

To track potential side effects, patients likely will have to undergo regular MRIs and PET scans on top of their monthly or twice-monthly drug infusions, Widera said.

"Even in people with mild dementia, it will not bring them back to where they were a year ago, two years ago. At best, it's going to slow down the rate of their decline," he said. "Now, for some people, that's really important for them, and they're willing to take risks and they're willing to put up with frequent MRIs, PET scans, monthly infusions with donanemab, twice a month with lecanemab. And for those individuals, it may be worth considering."

For others, not so much.

"For a whole host of other individuals, including people who are taking anticoagulation, people who are APOE4 homozygous, the risks are probably looking like they outweigh the benefit," Widera said.

At first, Mayo Clinic plans to offer anti-amyloid treatment only to patients who live within 100 miles because doctors want to follow them, Petersen said.

"We don't want to send them back to Mandan, North Dakota, and say, have your doctor keep an eye on the symptoms and the side effects," he said. "We want to do it here because, one, we want to learn about them, and two, for patient safety, we want our neuroradiologist to look at the MRI scans and we want our clinician to evaluate the symptoms. We're going to be quite conservative initially."

And that leads to one of Widera's biggest worries—that other medical centers won't be as stringent as Mayo.

"This is a highly regulated drug study where we're seeing these benefits

and they're closely monitoring for harms," he said of the donanemab trial. "Once this is in the wild, it is no longer so regulated. And if individuals can prescribe these medications without potentially any training, without setting up the proper systems in place for good monitoring, I worry about the outcomes for the people who are going to get these drugs."

On the other hand, editorialists said this also could mean that poorer people in rural areas who can't afford to travel to sophisticated centers will not have equal access to anti-amyloid treatment.

The Alzheimer's Association is dedicated to removing such obstacles and making sure the drug treatment is available to anyone who qualifies, Edelmayer said.

"Making sure that people do have access to life-changing medications is something that the Alzheimer's Association strongly stands behind," she said. "We continue to encourage coverage by the Centers for Medicare and Medicaid and all other insurance providers for these treatments, which are really aimed at treating a fatal disease."

As with any fatal disease, people should have options, she added.

"They should have the opportunity to talk with their doctors and have the opportunity to have access to these treatments, so that they have the opportunity to slow down their disease progression," Edelmayer said. "That's our goal."

More information: The Alzheimer's Association has more about lecanemab.