Lecanemab (Leqembi), the new Alzheimer's disease treatment: Information for families and patients

Knowing whether or not to use the new Alzheimer's Disease treatment lecanemab (trade name: Leqembi) can be a confusing decision for families, patients and health care professionals, especially with all the media attention the new product has received. Here, we summarize the most current, balanced evidence about its **benefits,** its **side effects,** and its **other burdens.**

Benefits of Leqembi

The drug, given intravenously every two weeks, was found in a clinical trial to slightly reduce the rate at which patients lose their memory. The study was done in patients with early Alzheimer's Disease or a less severe condition, Mild Cognitive Impairment (MCI), in which people have some memory problems but can take care of their basic daily needs on their own. It has not been shown to work in people with moderate or severe Alzheimer's disease.

Leqembi is not a pill; it must be given every two weeks through an intravenous (i.v.) "drip" over about an hour, for as long as the treatment continues. This must be done in a doctor's office, infusion center, or hospital. In the main study of the drug, it was given every two weeks for a year and a half. It isn't yet known how long these treatments have to continue beyond the 18 months studied so far.

The treatment does not make people's memory or mental functioning improve; instead, it slightly slows the rate of decline. The importance of this has been controversial. Some Alzheimer's experts were encouraged that even a very small effect is better than nothing. However, other experts were concerned that the difference was so minor that it might not even be noticed by many patients, families, or their doctors.

The main test used to study the drug evaluated performance on an exam that measured memory and other mental functioning. Nearly all patients in the clinical trial did worse at the end of 18 months than they did at its start, whether they took Leqembi or not. At the 18-month endpoint, the patients taking Leqembi lost about half a point less than those who didn't take the medicine, on a scale that went from 0 to 18. Some have said this could be seen as a 5-month delay in patients' decline, but others have questioned whether this small difference would be noticeable. The effect occurred primarily in men; for the women in the study, the benefit was much smaller, and was not significantly different from no treatment. Similarly, the effect in patients under age 65 was much smaller, and not significantly different from no effect.

Measuring amyloid levels before starting the drug

Because Leqembi is designed to destroy amyloid in the brain, it should be given only to people who have high brain amyloid levels. So before treatment is begun, a patient should have one of two tests to measure amyloid, along with an MRI brain scan.

- Test 1: PET scan (for Positron Emission Tomography). In this test, a special chemical is injected into the blood to measure amyloid levels in the brain. PET scanning equipment may be hard to find outside of large medical centers.
- Test 2: Lumbar puncture (a 'spinal tap'). In this test, a needle is inserted into the spinal cord area in the back to take a sample of the fluid that surrounds the brain.

In addition, before starting Leqembi patients should have an MRI brain scan; these tests are repeated periodically throughout the treatment, and more often if drug side effects are seen. To undergo a brain MRI, the patient's head is put in a plastic cage, and their body is passed into a small tunnel where powerful magnets spin around to create an image of the brain tissue. The test takes about 20 minutes, during which the patient has to remain motionless. The procedure is quite noisy, and patients are given ear plugs and headphones to make it more bearable. Some patients, especially older people with dementia, may not be able to tolerate the noise or become claustrophobic in the machine tunnel, and cannot complete the procedure. Sometimes sedation is required to enable people to finish the test.

After Leqembi is started, additional MRI brain scans are recommended during treatment (about once every 3 months for the first year, or more often for patients who develop worrisome symptoms). These scans check for the development of brain swelling and/or bleeding that might occur, even without symptoms.

Genetic testing

Some patients' genes may make them especially sensitive to the risks of brain bleeding or swelling when taking Leqembi, or less likely to benefit from it. *Apo-E* is a gene whose presence raises the risk of developing Alzheimer's disease, and *Apo-E*4 is one variant of this gene. People with at least one copy of the *Apo-E*4 gene, and especially those with two copies of it, are at much higher risk of having brain swelling or bleeding when given Leqembi. Furthermore, people with two copies of the gene, who could be at greater risk of memory loss, actually showed no benefit from the drug. As a result, the FDA suggests that patients be tested for *Apo-E*4 before being given Leqembi.

Side effects of Leqembi

About a quarter of patients given the drug had some kind of reaction to the i.v. treatments during the infusion, including fever or other flu-like symptoms such as chills, aches, feeling shaky, or joint pain. Between a third and a fifth of patients also had their white blood cell count drop initially when starting treatment. These problems usually improved in most people if they were able to continue taking the drug. Severe allergic reactions (hypersensitivity) also occurred in a very small number of patients, including potentially fatal complications.

Leqembi is an antibody created in hamster cells, and is designed to attack and destroy the amyloid protein in the brain. Many scientists think that the build-up of amyloid is the cause of Alzheimer's Disease. However, some patients with Alzheimer's Disease may not have much amyloid buildup, and some patients with amyloid in their brain do not have any symptoms.

When the antibody in Leqembi attacks amyloid, it can sometimes cause new problems, including swelling of the brain and small areas of brain bleeding. This occurs in about a fifth of patients given the drug, or about double the rate seen in comparison patients. This swelling or bleeding often causes no symptoms, or it can lead to headache, confusion, dizziness, vision changes, nausea, difficulty speaking, weakness,

or seizures. Besides the regular repeat MRI brain scans needed throughout treatment, additional brain MRIs are needed in patients who develop these symptoms to make sure these changes are not continuing or getting worse. Such side effects don't occur in all patients, and can often be relieved if the drug is stopped or the dose reduced. However, sometimes these areas of brain bleeding can become bigger; this problem appears to be rare, but it is not yet clear how often it occurs. A small number of patients taking Leqembi along with anti-coagulants (blood thinners) have had serious strokes leading to death. More needs to be learned about whether and how much anticoagulant drugs may contribute to brain bleeding risks in people taking Leqembi.

Over time, patients in studies of amyloid-attacking drugs like Leqembi have been found on average to have loss of brain volume, compared to subjects given comparison treatments. It isn't known what problems, if any, this can cause.

Treatment with Leqembi requires a multidisciplinary team to administer the drug safely. Primary-care doctors will need to refer patients to dementia specialists, who can help access PET scans, lumbar punctures, and MRI scans and make the decision on whether Leqembi is appropriate. Medicare will require that all patients prescribed Leqembi must be enrolled in a nationwide registry to gather more information on its effects and risks.

How much does Leqembi cost?

The expense of Leqembi may be an important factor for some patients and families. Its manufacturer has set a list price for the drug of $26,500 per patient for each year of treatment; that does not include the additional costs of doctor visits, tests, and infusion charges required, which have been estimated at about $7,300 more per year – making for a total of $33,800 per year. Medicare will pay for 80% of these tests and of the drug cost for people with "Part B coverage," with the rest of the bill potentially payable by the patient. Many patients in Medicare have supplemental ("Medigap") coverage that can help pay that amount, or they may be enrolled in a "Medicare Advantage" or retiree health insurance plan that may do so, but not all people will have such supplementary coverage. One estimate found that for some patients, their share of the total bill could be as high as $6,600 per year. The nation as a whole could pay between $2 billion and $5 billion annually for the drug.

Summary

The most important foundation for the care of a patient with memory loss is a thorough evaluation to search for potentially treatable causes other than Alzheimer's Disease, such as medication side effects, depression, or other medical conditions. These should be addressed before considering any new drug. For patients with Alzheimer's disease, the most important thing is to help families and caregivers understand that this is a disease that will usually get worse with time – and it is important to plan ahead and help patients achieve the best quality of life possible.

The world has been waiting many decades for an effective, safe, and affordable medication to address the devastating condition of Alzheimer's Disease. If Leqembi had a reasonably useful impact on the condition, were acceptably safe, and didn't put a severe burden on patients, caregivers, and the health care system, it would really be the important step forward it has been said to be. In the end, it might still be a reasonable choice for some patients and families who are willing to deal with its potential downsides in their quest to slow the pace of this cruel disease, however slightly. But other families, patients, and

medical professionals will weigh its limited benefits, worrisome risks, and substantial toll on patients and the Medicare program as a whole, and conclude that the tradeoff may not be worth making.

More information on Alzheimer's disease and what to know in caring for older patients with cognitive impairment is at: AlosaHealth.org/dementia/

These materials for families and patients will be updated as new information becomes available.

These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.

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