Patient Focused Decision Guide
When Considering Infused Amyloid Reducing Drugs for Alzheimer's Disease

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Being diagnosed with Mild Cognitive Impairment (MCI) or mild dementia due to Alzheimer's Disease (AD) can be emotionally overwhelming. Until very recently there were no treatments available to slow the disease's progression. The new drug treatments are complex. They are monoclonal antibody (MAB) immune therapies. The drugs reduce amyloid plaques within the brain. These new drugs have testing requirements, both before and after starting treatment. They may not be the right choice for everyone. There are a number of benefits and risks to consider.

This decision guide is written to assist you, the patient, and your support/care partners, with the discussion with your doctor to pursue treatment with these new drugs. We use the term support partner for anyone involved in supporting you, the person with a diagnosis of MCI or mild dementia due to AD. This decision guide is prepared by actual patients and support partners who have considered these drugs and have taken part in the clinical trials. This decision guide is to help you discuss your questions and concerns with your doctor. It is not intended to explain medical issues or answer questions about the drugs or Alzheimer's Disease. Take all the time you need to make this decision together with your support partner and doctor or doctors. We have written this document with the aim to keep it short and focused on your decision to consider these new infused drugs for slowing MCI or mild dementia due to Alzheimer's. There are a number of links for more information at the end. Your doctor is your best source for information.

There now are several new amyloid reducing monoclonal antibody drugs available for the treatment of MCI or mild Alzheimer's disease. While not a cure, extensive clinical trial research with patients show that these drugs slow the progression of the disease. These drugs presently include Leqembi (lecanemab) and a similar drug expecting approval in 2024 (donanemab). The drugs are available for patients considered eligible by their doctor. They also have risks that require safety checks with frequent MRIs and bloodwork. The treatment has a demanding schedule of bi-weekly or monthly on-site IV infusions. Any safety issues seen during treatment may require additional safety checks.

Entering into treatment with an amyloid reducing drug is a major decision with important considerations because of time demands and side effects. These drugs offer the hope of life-enhancing results for individuals with MCI and mild dementia due to AD.

Taking charge of your decision

The decision is a process with multiple steps. These drugs offer hopeful treatment for slowing AD, but only for those who are likely to benefit while reducing risk where possible.

1. First you will need to find a doctor qualified to diagnose MCI and mild dementia due to AD and to prescribe amyloid-reducing drugs. You will also need to identify a support partner that can be there for you while you have treatment. A support partner does not have to be a family member, they can be a friend or even paid caregiver.
2. Next, it will be important to understand the requirements to receive these drugs. There are several steps and tests needed to determine if you are eligible. You will discuss with your doctor your diagnosis, current and past health conditions, other medications you are taking, presence of amyloid plaques, genetic markers, tolerance for MRIs and infusions, and availability to follow the treatment schedule.

3. Finally, you will need to weigh the benefits and risks of this treatment. While important, this document does not address financial costs or insurance coverage for treatment.

Different doctors may have different requirements for who can receive these drugs. A detailed list of typical criteria for determining eligibility is listed below in Table 1. These are the specific criteria for Leqembi. Other anti-amyloid drugs may have similar requirements.

Table 1: What is required and not allowed for Leqembi?

Required

1. Diagnosis of MCI or mild dementia due to Alzheimer's disease with some memory impact. Your doctor may require a score of 22-30 on the Mini-mental state exam (MMSE).
2. Confirming elevated amyloid in brain. This will be measured either with a PET scan or lumbar puncture to look at Cerebral Spinal Fluid (CSF).
3. Age between 50-90, with doctor discretion outside this age range
4. Not extremely over or under weight, determined by your doctor
5. Able to tolerate MRI and PET scans (no claustrophobia, metal implants, pacemakers, etc). Music or medication may be available to help.
6. Commitment of patient and support partner to treatment and safety schedule. This is important for your safety and a successful treatment.
7. Genetic testing for the APOE gene may be required. If not required, consider learning your genetic status to help you weigh the risks and benefits. Learning your APOE genetic results is not trivial, and may bring concern, or relief, to you and your blood relations. You and your family can ask for genetic counseling. Here's a tool to help you think through APOE testing: https://genetestornot.org/

Disqualifying factors

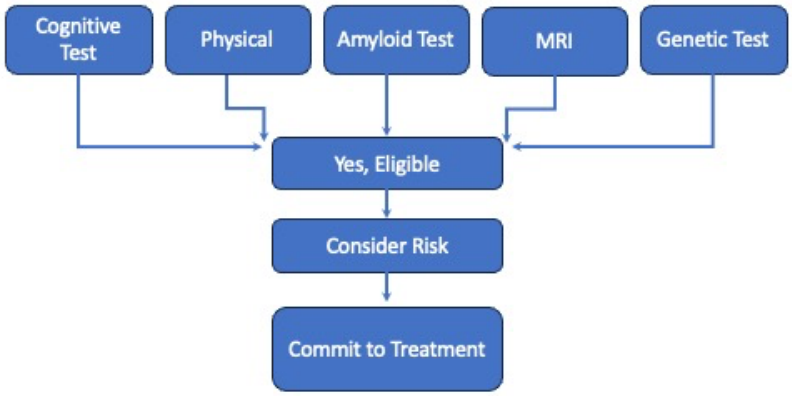
1. Cognitive loss from causes not related to AD.
2. MRI showing history of brain bleeds, multiple microhemorrhages, strokes, inflammation or other concerns in the brain. These need careful review with your doctor to see if outside the safety parameter for prescribing the drug. Less than 4 microhemorrhages may not be disqualifying.
3. Any mini-strokes, transient ischemic attacks (TIA), or seizures in past 12 months.
   Poorly controlled depression or other mental illness
4. Any history of immune disease such as rheumatoid arthritis, Lupis, or Crohn's disease.
5. Drug treatments with immunosuppressants, or immunoglobulins, or other MABs.
6. Bleeding disorders not fully under control.
7. Use of blood thinners such as Eliquis or Xarelto, coumadin, heparin, and several other anticoagulants.
8. Unstable medical conditions such as cardiac, respiratory, gastrointestinal, or renal diseases that are not adequately controlled.

Questions to discuss with your doctor:

- Does my doctor/health system have any other requirements I should know about?
- What are the steps for evaluating if I'm eligible for these new drugs? In what order will they happen?
- How long will it take to complete these steps?

Once your doctor has confirmed you are eligible, you will need to consider the benefits and risks.

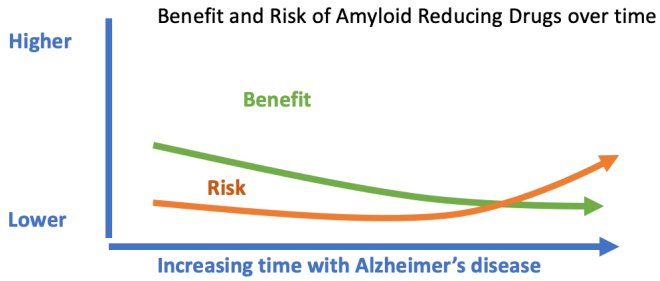
Figure 1. The Decision Process



WHAT ARE MY BENEFITS?

These drug treatments are shown to slow the loss of memory and thinking skills in patients with MCI and mild dementia due to AD. The benefits might be prolonging your independence and maintaining quality of life for yourself and those around you. This might include prolonging the time you're able to drive, shop, handle your financial affairs, enjoy your favorite activities, dress, maintain personal hygiene, and participate in complex conversations and decisions. Benefits are individual and are based on your starting point and overall health. While these drugs are not a cure, extending your quality of life for months or even a few years may be a meaningful benefit. Many clinical trial participants took these drugs for a length of time, and a large number of them and their support partners saw the benefit received with sustained quality of life.

Evidence is showing that the earlier in the disease one begins treatment to remove amyloid, the greater the benefit in slowing loss of thinking and memory. An early MCI patient is expected to have slower decline and longer benefit than a patient with mild dementia due to AD, though both may benefit. You may experience better or equal results depending on your personal starting point with the disease.



MCI and Alzheimer's disease cause gradual changes to memory and thinking. It is possible that you may not notice a difference while taking these drugs. The drugs do not improve memory and thinking, but slow decline. The effect of these drugs was seen in research when comparing two large groups of people, those taking the drug and those taking placebo. The participants had a wide range of starting scores on cognitive tests, health states, and AD assessment. These drugs are also new. With more experience we will learn more about what types of people are more likely to benefit, and the best way to measure whether the drug is working.

Over time Alzheimer's Disease advances. As the graph illustrates, there may be a future time when the potential helpfulness of the drug does not outweigh possible risks. Your doctor may decide to discontinue treatment at this point. It is also possible that drug will be stopped after most amyloid plaque is removed from the brain.

WHAT ARE MY RISKS?

Like most drugs, and especially these, there are risks. These can be levels of discomfort or reaction at the infusion site. It might be within the brain itself reacting to the removal of amyloid plaque. Research studies were done to verify the effectiveness of these drugs and to measure risk for side effects. The FDA approves a drug when risks are well understood, and are considered manageable when compared to the benefit of treatment. FDA approval does not mean the risk is nonexistent or not concerning to you.

When making this decision, you will want to understand your personal risk for side effects. There is meaningful difference in risk that is based on your APOE genetic status. This should factor into your decision on risk and discussed with your doctor. Your APOE gene status is determined by a blood test. It is important to know because the particular copy of the APOE gene you carry can influence your risk for side effects with these new drugs. Your doctor can explain this further when your APOE gene status is known. The results from clinical trials are published in scientific journals and are publicly available. Do not hesitate to ask your doctor about the side effects that were seen in research studies, especially for people with your genetics and health conditions.

Further below are some questions you might use to discuss your benefits and risk with your doctor. There is a great deal of information, accurate and also unverified, on the internet. Be diligent in seeking information that is from a qualified provider. **Ask for information from your doctor who will know you and your circumstances best. It is important to have open communication with your doctor because it is necessary to share your experiences and possible side effects with your doctor. You and your loved ones are your best advocate for your safety.**

TYPES OF RISK

In the clinical trials for these drugs the main side effects were ARIA events (Amyloid-Related Imaging Abnormalities). These events included brain swelling or edema, known as ARIA-E, or micro level brain bleeds or hemorrhages known as ARIA-H. Most of these events were not noticed by patients and only discovered during MRI safety checks. For a small number of patients these events were noticeable and reported to their doctor. ARIA symptoms can include headache, confusion, dizziness, visual changes, nausea, weakness, trouble speaking, and gait difficulty. When ARIA events were found, usually on an MRI safety scan, patients were either temporarily or permanently removed from treatment. In nearly every case the ARIA resolved on its own after stopping treatment. Pausing treatment and further monitoring were for patient safety. This is the purpose of the scheduled MRI safety checks while on treatment.

Serious risk of the drug is uncommon but can occur. These risks include seizures, stupor, macro-hemorrhage (large brain bleed) and other neurological concerns. In the extreme, death may occur. Serious incidents are very few, and usually these events occur in the individuals with higher likelihood of risk, because of their genetics, other prescribed drugs, or health and lifestyle factors.

Lesser risks include infusion reactions. In the Leqembi study these tended to occur during the first two infusion treatments and involved about a quarter of patients (25%). Typical symptoms were fever, chills, headache, rash, nausea, vomiting, abdominal discomfort, and elevated blood pressure. Treating with Tylenol and Benadryl/Zyrtec before an infusion could help prevent these symptoms.

Questions to help you weigh risks and benefits

- With my diagnosis and age, what is the possible benefit of this drug?
- If I don't take this drug, what changes should I expect over the next year or two?
- How long might I expect to stay on the drug?
- What should I and my support partner be looking at to decide whether to stay on or discontinue this drug?
- What is my risk for side effects? Here's a list of my health conditions and medical history. Were people like me included in the research?
- Here's a list of medications I'm taking. Do any of these medications change my risk for side effects?
- How will you check to make sure this drug is safe for me?
- If I think I'm having a side effect, should I go to the ER? How do I report side effects to you?

COMMITMENT TO A TREATMENT OF INFUSED AMYLOID REDUCING DRUGS

Treatment with infused drugs requires substantial commitment. There is a multi-step, multi-visit process for determining eligibility. This includes cognitive testing, health assessment, MRI, PET scan or CSF test (lumbar puncture), and genetic testing. Infusions are biweekly for Leqembi and monthly for donanemab. They are administered at approved infusions sites. The visits are usually over an hour in duration. There are periodic MRI safety checks. This is an extensive amount of your and perhaps your family member or care partner's time. Time is devoted to screening visits, infusions, periodic safety checks and MRIs, and travel to medical appointments. Fulfilling the commitment to the treatment protocol, bi-weekly or monthly, is necessary. Any safety issues that are flagged will involve additional visits for further safety monitoring. While substantial, the commitment is comparable to the commitment required of similar drugs used in other diseases.

What if I don't qualify for this treatment?

- Stay in touch, these criteria may change over time as more is learned.
- Consider signing up for a research study.
- Stay tuned, more drugs are being tested

PARTING THOUGHTS FROM THE AUTHORS OF THIS DECISION GUIDE

As people living with a diagnosis of AD and support partners, we are excited to welcome this new era of treatments. This is the first time a proven treatment exists which offers extended independence and quality of life to people diagnosed with MCI and mild dementia due to AD. The future is promising. In the next year or two we hope to see advances that make it easier to use these drugs. The advances include self-injected drug rather than IV infusions. Blood tests to measure amyloid may soon be approved and replace the required PET scans and lumbar punctures. These possibilities are under FDA review but not yet approved. There are also many additional treatments under study that may become available in the next years.

This document was prepared by a subcommittee of the Alzheimer's Clinical Trials Consortium (ACTC) Research Participant Advisory Board. Contributors include A. Aldebol, D. Chan, N. Childs, R. Long, N. Meserve, S. Walter. Direct questions to S Walter, MSc, ACTC Program Administrator, at waltersa@usc.edu. Version 1. February 2, 2024

Glossary

AD: Alzheimer's disease. The most common type of dementia estimated to affect 6 million people in the US.
Amyloid plaques: an accumulation of misfolded proteins in the brain that are thought to have a central role in Alzheimer's disease.
APOE: Apolipoprotein E is a gene that influences Alzheimer's risk.
ARIA events: Amyloid-Related Imaging Abnormalities (ARIA) is seen with MRI brain imaging.
CSF: Cerebral Spinal Fluid is collected using a lumbar puncture and can be used to measure amyloid in brain.
FDA: Food and Drug Administration. Reviews results of research and approves drugs for clinical use.
MAB: Monoclonal Antibodies are proteins made in laboratories that act like proteins called antibodies in our bodies. MABs target specific amyloid proteins in the brain.
MCI: Mild cognitive impairment is an early stage of memory or cognitive ability loss while able to independently perform most activities of daily living
MMSE: Mini-Mental State Exam is a set of questions commonly used to check for cognitive impairment.
MRI: Magnetic Resonance Imaging measures brain volume and is used to monitor changes in brain and check for side effects due to amyloid treatment.
PET: Positron Emission Topography. Amyloid PET scans are used to measure amyloid in brain.

Additional resources

How and why to get a diagnosis for MCI or Alzheimer's disease:
https://www.alz.org/alzheimers-dementia/diagnosis

Finding a doctor:
Choosing a doctor to evaluate memory and thinking problems is a May 2023 PDF from the Alzheimer's Association, an explanation of the typical process and types of doctors.
Community Resource Finder is a joint resource from the Alzheimer's Association and AARP that provides a list of neurologists with name, address, phone number within 25 miles of a zip code or city. Users can also search for geriatricians, geriatric psychiatrists and hospitals. Note: Click on https://www.communityresourcefinder.org and then on the box labeled MEDICAL SERVICES, Check Neurologist and enter your zip code.

What happens to the brain during Alzheimer's disease, and the role of amyloid:
https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease

What are current treatments for Alzheimer's:
https://www.alz.org/help-support/i-have-alz/treatments-research

Appropriate Use Guidelines for Leqembi – written by doctors and researchers to help guide medical providers in the use of Leqembi. https://link.springer.com/article/10.14283/jpad.2023.30

Genetic testing resources:
A tool to help you and blood relatives think through APOE testing: https://genetestornot.org/

Locate Genetic Professionals in your Area:
National Society of Genetic Counselors: https://www.nsgc.org/