Using Leqembi to Delay Progression of Early Alzheimer's Disease

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Executive Summary

Current treatments for AD include symptom management for both cognition and behavior. Common theories surrounding the cause and treatment of AD include Aβ plaques and neurofibrillary, or tau, tangles in the brain. Leqembi (lecanemab-irmb) reduces Aβ plaques. This paper will discuss the criteria and use of Leqembi for the treatment of early AD with confirmed brain amyloid pathology.

Acronyms	
AD	Alzheimer's disease
ADAS-Cog14	Alzheimer Disease Assessment Scale – Cognitive Subscale 14
Aβ	Amyloid beta
APOE	Apolipoprotein E gene
ARIA	Amyloid-related imaging abnormalities
ARIA-E	Amyloid-related imaging abnormalities with edema
ARIA-H	Amyloid-related imaging abnormalities with hemosiderin deposition
CDR-SB	Clinical Dementia Rating Sum of Boxes
CMS	Centers for Medicare and Medicaid Services
CSF	Cerebrospinal fluid
FDA	Food and Drug Administration
IV	Intravenous
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
tPA	Tissue plasminogen activator

Leqembi – Things to Consider

- Leqembi is not a cure for AD, but it has been proven to slow the rate of cognitive decline of the disease in its early stages.
- Patients must be referred to a neurologist or neuropsychiatrist to be diagnosed with AD and prescribed Leqembi.
- Leqembi reduced Aβ plaques in a dose- and time-dependent manner.
- Leqembi is an Aβ-directed monoclonal antibody administered by IV, infused over one hour every two weeks.
- MRI monitoring is required prior to and throughout the first year of treatment.
- Patients on anticoagulants would not be eligible for treatment. If patients are being treated with Leqembi and need to take an anticoagulant for a new medical condition, they should stop Leqembi treatment.
- Due to increased risk of bleeding, patients with cerebral amyloid angiopathy identified on initial MRI would not qualify for treatment.

Key Patient/Caregiver Talking Points

- Patient commitment is essential. Pretreatment workup is required with lab testing, baseline MRI and a lumbar puncture. The treatment process is standardized and requires every two-week infusions, along with neurologist visits and brain MRIs at predetermined intervals.
- Cost of medication is expensive, but the patient also needs to consider cost of monitoring and administration.
- Weigh risk versus benefit
    - Risk
        - Infusion-related reactions occurred in 26.4% of patients.
        - ARIA with edema or effusions occurred in 12.6% of patients.
        - For patients who are on or who may require anticoagulants/antithrombotics – roughly doubled the risk of ARIA and potentially may increase the risk for intracerebral hemorrhage when used in combination with Leqembi.
    - Benefit
        - Although outcomes regarding rate of decline in cognition were statistically significant in the studies, the clinical benefit is likely marginal.
        - Patients treated with Leqembi still experienced decline in cognition and function but at a rate less than placebo.

- There was clinically significant reduction in plaque seen on imaging.

Table 1: Quick Facts About Leqembi

Therapeutic class	Aβ-directed monoclonal antibody
Use	Treatment of early AD (efficacy has not been studied in moderate to severe AD)
Dosing	10 mg/kg IV every two weeks, infused over one hour
Mechanisms of action	Reduces the number of aggregated and insoluble forms of Aβ

Adverse reactions	• Infusion-related reaction (fever and flu-like symptoms, nausea, vomiting, hypotension, hypertension, and oxygen desaturation)
	• ARIA
	  ○ Usually asymptomatic
	  ○ Reported symptoms may include headache, confusion, visual changes, dizziness, nausea, and gait difficulty
	  ○ Serious and life-threatening events, including seizure and status epilepticus, rarely occur
	• Headaches

Monitoring parameters	• MRI monitoring prior to initiation and throughout the first year of treatment • Surveillance MRIs: baseline, prior to fifth, seventh and 14th infusions to evaluate for ARIA
Prescriber	Neurologist with a referral
CMS considerations	• CMS confirmed they will cover Leqembi broadly under Medicare • Prescribing providers must participate in the CMS National Patient Registry To receive Medicare coverage: • Must be enrolled in Medicare • Must be diagnosed with MCI or mild AD with appropriate biomarker positivity (amyloid PET or CSF tau/amyloid) • Have the provider participate in a qualifying registry with an appropriate clinical team and follow-up
Duration of treatment	Recommend discontinuation of Leqembi once the patient reaches the moderate stages of AD
Cost	• Estimated medication cost of $26,500 per year based on an average patient weight of 75 kg • Medication is expensive but is only a portion of the cost as monitoring and administration are also expensive

Clinical Study Data

Efficacy

Study 1 (Swanson 2021)

- Results showed that Leqembi had a 64% likelihood of ≥25% slowing of progression on the primary endpoint relative to placebo at 53 weeks
  - Primary endpoint: change from baseline on a weight composite score of items from the CDR-SB, MMSE and ADAS-Cog14
  - This did not meet the prespecified success criterion of 80%
- Leqembi had a statistically significant reduction in brain amyloid plaque at week 79 compared to placebo

Study 2 (van Dyck 2023)

- The CDR-SB score increased by 1.21 in the Leqembi group compared to 1.66 in the placebo group at 18 months (95% confidence interval, -0.67 to -0.23; P<0.001)

  - A definition of clinically meaningful effects of the CDR-SB score has not been established
  - Primary endpoint: change from baseline to 18 months of the CDR-SB
- A statistically significant reduction of amyloid burden was seen in the Leqembi group compared to placebo

Safety

Black Box Warning

- May cause ARIA, ARIA-E and ARIA-H. Although rarely serious, life-threatening events can occur
- APOE ε4 homozygotes have increased risk of ARIA, so genetic testing should be completed prior to initiating treatment
  - Approximately 15% of AD patients are homozygous for APOE ε4
  - Homozygotes have double the risk of ARIA. Symptomatic ARIA-E and serious events of ARIA occur more frequently compared to heterozygotes and noncarriers

Study 2 (van Dyck 2023)

Side effect	Leqembi	Placebo
Symptomatic ARIA* Serious symptoms associated with ARIA	3% (29/898) 0.7% (6/898)	
ARIA (including asymptomatic and symptomatic)	21% (191/898)	9% (84/897)
ARIA-E	13% (113/898)	2% (15/897)
ARIA-H	17% (152/898)	9% (80/897)
Intracerebral hemorrhage >1 cm in diameter	0.7% (6/898)†	0.1% (1/897)

*Clinical symptoms associated with ARIA resolved in 79% (23/29) of patients during the period of observation
†Fatal events of intracerebral hemorrhage in patients taking Leqembi have been observed

Intracerebral hemorrhage

- Additional caution should be exercised when considering the administration of anticoagulants or a thrombolytic agent to a patient already being treated with Leqembi.
  - Although not absolute contraindications, neurology recommends against use of:
    - Thrombolytic agents (i.e., tPA) when a patient is receiving Leqembi
    - Concomitant anticoagulation (i.e., would discontinue Leqembi in a patient starting anticoagulation, or would not prescribe Leqembi in a patient on an anticoagulant)
- In the clinical trial, use of antithrombotic medication (aspirin, antiplatelet agents, or anticoagulants) was allowed if the patient was on a stable dose.

Leqembi Pathway – Avera Primary Care Process

Symptoms of Alzheimer's Disease

Patients that present with the following symptoms should be assessed for referral to neurology for diagnosis of AD. The symptoms include, but are not limited to:

- Forgetting recent conversations or events
- Misplacing items
- Forgetting names of places and objects
- Becoming lost in familiar places
- Asking repetitive questions
- Having difficulty thinking of the correct word

Primary Care Assessment for Cognitive Decline

Once cognitive decline is suspected, the primary care provider will administer the MMSE. The MMSE is a screening tool used to test for cognitive impairment. It consists of 11 questions with varying point values with scores ranging from 0-30. The MMSE is not built into MEDITECH. Providers will need to complete this on paper and scan into the patient's chart.

There is a MMSE option within 'Questionnaire' in MEDITECH which will allow the provider to document the overall score. Cognitive functioning is characterized into one of five domains (learning and memory, language, visuo-spatial, executive and psychomotor). The MMSE scores are ranked as follows:

- 27-30: Normal cognitive function
- 21-26 (only 1 cognitive domain involved): Mild cognitive impairment
- 21-26 (>1 cognitive domain involved): Mild dementia
- 11-20: Moderate cognitive impairment
- 0-10: Severe cognitive Impairment

If the results of the MMSE show mild cognitive impairment or mild dementia, the primary care provider discusses therapies with the patient. If the patient decides to proceed, the primary care provider will order an MRI and labs through an order set (there will be order sets and a process map built into MEDITECH to further guide the process for referral). If test results show abnormalities, primary care will treat and then reassess cognition after treatment. If test results are within normal ranges and normal result on MRI, primary care will speak to the patient about results and get their decision to proceed with a referral to neurology.

Diagnostic Criteria for Alzheimer's Disease

An AD diagnosis will be made by a neurologist or neuropsychiatrist following a referral. An MRI, PET scan or lumbar puncture are the common methods to screen for biomarkers of AD alongside the gradual cognitive decline. The criteria include, but is not limited to:

- Presence of biomarkers associated with AD
    - Aβ plaque accumulations
    - Tau depositions in the neurofibrillary tangles associated with neuronal degradation or injury
- Symptoms of AD (mentioned above)

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