Health Monitor®

Clinician Update

MCI and Alzheimer's Disease

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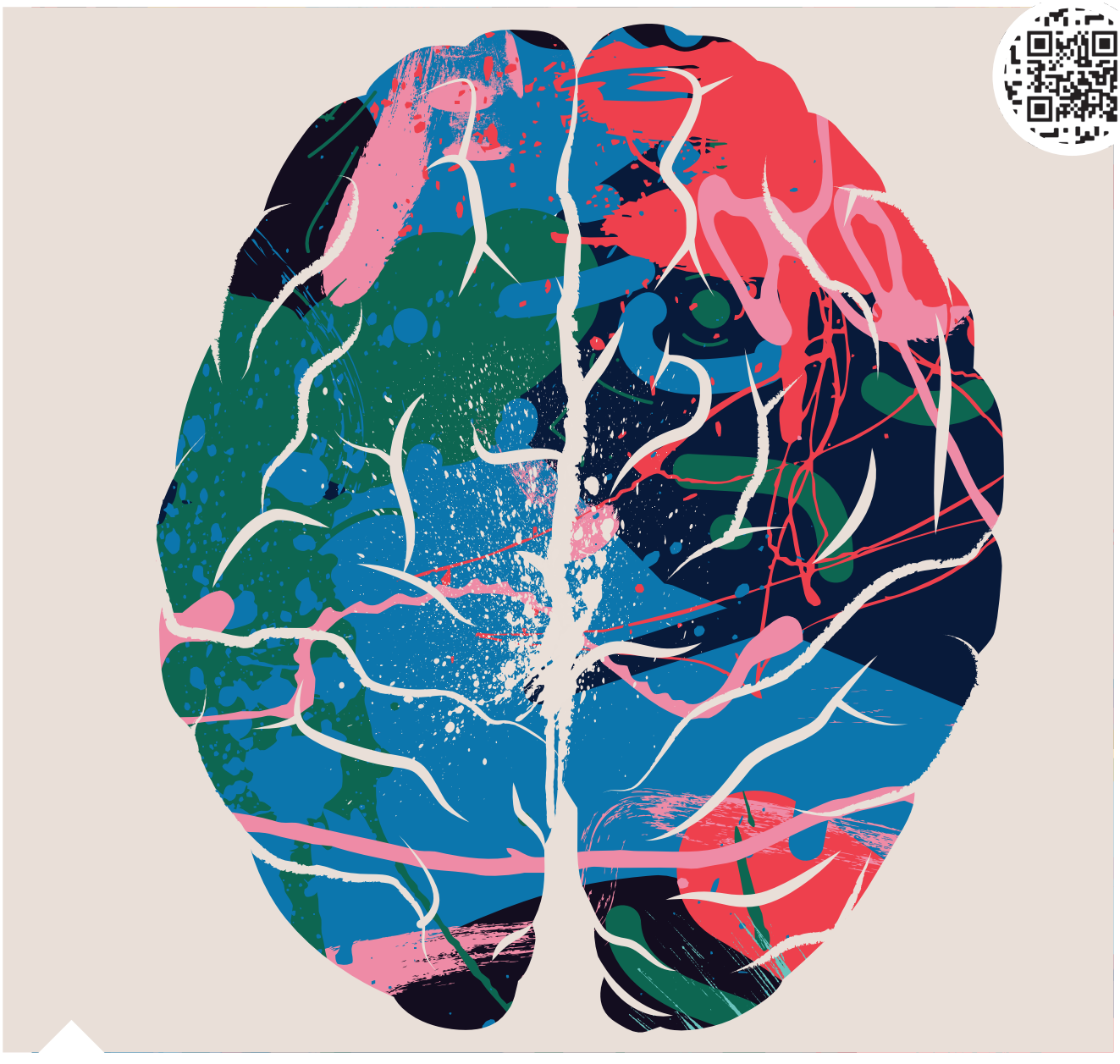

The amyloid-beta pathway: a key player in the pathogenesis of AD

Experts now know that Alzheimer's disease is decades in the making—and one of the main culprits is the accumulation of amyloid-beta that triggers downstream effects and, ultimately, neurodegeneration.

For decades, clinicians have been unable to offer a treatment to slow the cognitive and functional decline of their patients with Alzheimer's disease (AD). Cholinesterase inhibitors are formulated to preserve memory by preventing acetylcholine breakdown, but these agents lose effectiveness as the disease progresses and less acetylcholine is produced.[1] The N-methyl-D-aspartate receptor antagonist memantine has shown some clinical benefit in moderate-to-severe AD but no efficacy in early-stage AD.[2]

Investigators, however, have continued to search for answers, probing alternative treatment targets to attempt to slow or even halt AD's debilitating effects. One such target, the amyloid-beta cascade, is in the forefront of research. Through this pathway, amyloid-beta proteins proliferate, aggregate and lead to amyloid plaques and, ultimately, tau tangles that diminish cognition and function. Newer agents on the market and in the pipeline have shown efficacy in mild-to-moderate AD by targeting this pathway and eliminating amyloid plaques, and these findings are providing patients and their families with new hope against a difficult-to-manage disease.

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Illustration by John Holcroft / ikon images

"It is essential to control amyloid-beta as the place to start to find the right therapy to prevent or treat dementia," says Samuel E. Gandy, MD, PhD, Professor of Alzheimer's Disease Research and Associate Director of the Alzheimer's Disease Research Center at Mount Sinai Medical Center in New York City.

The amyloid-beta cascade

Researchers have been following the amyloid-beta pathway since the mid-1980s, when the protein and its amino acid sequence were strongly associated with Down syndrome and, soon after, AD.[3] Through the 1990s and early 2000s, studies that focused on autosomal dominant AD genes, genetic risk factors for amyloid-beta accumulation and AD-related biomarkers, provided evidence that AD pathophysiology begins to develop decades before the onset of symptoms.[3]

"There are believers in this hypothesis, and there are disbelievers," says Pierre N. Tariot, MD, Institute Director of the Banner Alzheimer's Institute in Phoenix and Co-director of the International Alzheimer's Prevention Initiative. "The bottom line is that there is strong genetic evidence that amyloid is in some cases sufficient to cause Alzheimer's dementia and in other cases necessary, but some say that this hasn't been fully determined."

What is known is that many people accumulate amyloid deposits in the brain as they age. As part of the normal molecular life cycle, the amyloid precursor proteins (APPs) from which amyloid-beta is developed are cleaved by alpha-secretase proteolytic enzymes, resulting in harmless amyloid fragments. Alternatively, some APPs are processed by gamma-secretase and beta-secretase enzymes, causing the resulting amyloid fragments to misfold and proliferate, leading to an imbalance in amyloid-beta production and breakdown common among people with AD.[3]

Misfolded amyloid-beta proteins initially are produced as soluble monomers; these monomers then proliferate and aggregate into larger soluble forms, including dimers and trimers, oligomers and protofibrils. Some of these aggregations later become insoluble fibrils that ultimately develop into insoluble plaques; both formations are associated with synaptic dysfunction in AD.[3]

Aside from proliferation, other factors that contribute to brain amyloid-beta buildup in AD include changes in receptor expression that dictate amyloid-beta movement between the brain and blood, as well as altered flow and absorption of cerebrospinal fluid during aging.[3]

Figure 1.

Stages of Alzheimer's disease: amyloid-beta deposition over time[3]

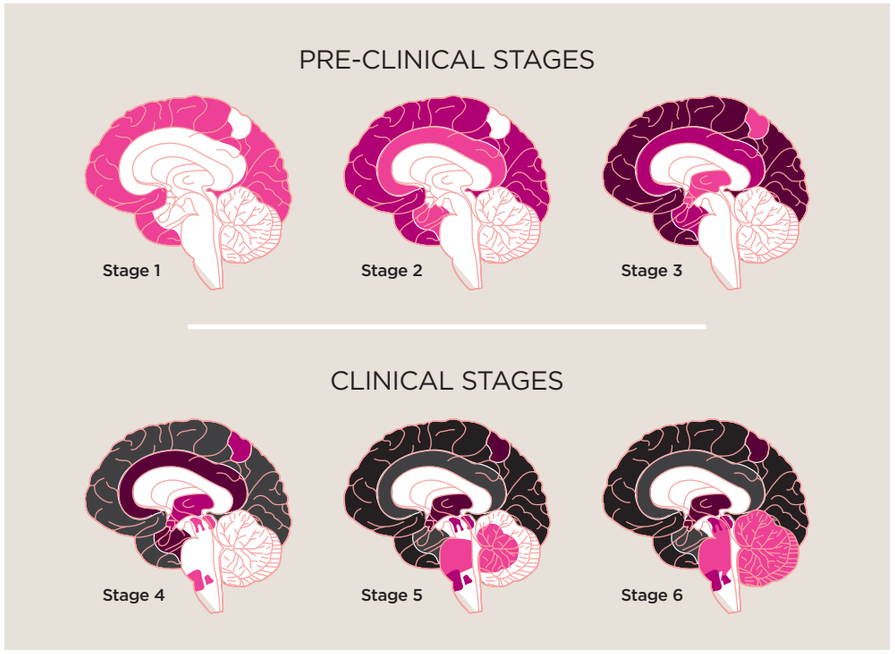

Illustration by Juhee Kim

Plaque development and AD: decades in the making

As amyloid plaques keep developing and proliferating into an "amyloid bloom," Dr. Tariot notes, they initiate the abnormal processing and accumulation of tau proteins and, ultimately, tau tangles. "It's the tangle severity, not the amyloid burden, that is correlated with the degree of cognitive impairment in a patient who has symptoms," he adds.

Through decades of investigation, researchers identified amyloid protein accumulation in the brain as an upstream process that begins decades before AD symptoms develop (see Figure 1). This has led investigators to hypothesize that if the amyloid-beta cascade and plaque production could be detected and disrupted, the progression of AD and its devastating effects could be delayed and perhaps halted.

Researchers have responded by developing agents formulated to disrupt specific segments of the cascade. Since 2016, several molecules have been created to either prevent amyloid proteins from aggregating or inhibit the beta-secretase and gamma-secretase enzymes that misfold amyloid proteins. But so far, neither mechanism of action has shown efficacy in slowing AD-related cognitive and functional decline.[4]

A novel approach to slowing progression

A more recent mechanism for disrupting the pathogenesis that leads to plaque has involved development of amyloid-targeting agents, synthetic monoclonal antibodies that interact with different aspects of the cascade and prompt the immune system to detect and destroy soluble and insoluble amyloid formations, including plaques. While earlier amyloid-targeting antibodies have not shown efficacy, more recently developed agents in this class have been shown in clinical trials to slow clinical progression of early-stage AD compared with placebo.[5-8]

"In an 18-month trial period, persons on one of these agents are likely to have about 5 to 6 more months of preserved higher level of functioning compared with patients not receiving the treatment," Dr. Tariot says. "That is, patients receiving these agents are about a third better off after 18 months, and there is thinking that if the treatment were to be continued, that treatment difference might continue to increase over time."

> "THE DATA ON TREATMENTS TARGETING AMYLOID-BETA ARE VERY ENCOURAGING. IT IS THE MOST HOPEFUL MECHANISM OF ACTION WE HAVE SEEN SO FAR."
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> —Samuel E. Gandy, MD, PhD

Adds Dr. Gandy, "The data on treatments targeting amyloid-beta are very encouraging. It is the most hopeful mechanism of action we have seen so far."

Caution is necessary in certain patient populations

It is important to note that amyloid-targeting antibodies carry a risk of amyloid-related imaging abnormalities (ARIA), which is the most common adverse effect of these agents. ARIA is believed to be caused by neuroinflammation or vascular rupture associated with plaque removal.[9]

ARIA is usually asymptomatic, but in some cases, it can cause headaches, worsening confusion, dizziness, visual disturbances, nausea and seizures.[9] It is most commonly associated with edema (ARIA-E) or hemorrhage (ARIA-H); either subtype has been reported in about 40% of

patients receiving these agents based on imaging tests, with one-quarter of patients reporting symptoms.[10]

Researchers also have found that ARIA-E is more prevalent at treatment initiation, at higher dosages, among patients with more than four microhemorrhages at baseline, and among patients who carry the ApoE4 gene.[9] Therefore, genetic testing for the ApoE4 gene is strongly recommended before administering an amyloid-targeting antibody, Dr. Tariot advises. In addition, studies have found that the risk of ARIA-H increases with age and cerebrovascular disease.[9]

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Promising studies continue to explore anti-amyloid therapies

Targeting the amyloid-beta cascade holds significant promise for AD treatment and is among the most common mechanisms of action of AD agents now in development. About 25 therapies targeting different aspects of the cascade are in various clinical trial stages, as are agents that target alternative pathways associated with AD pathophysiology such as inflammation, oxidative stress and synaptic function.[11]

Currently, anti-amyloid antibodies are administered by intravenous infusion, but subcutaneous formulations also are being developed. One subcutaneous molecule has received FDA fast-track designation,[12] while others are in early-stage clinical trials. "This could be a major game-changer," Dr. Tariot says. "Patients wouldn't need to go into an infusion center. You could use an autoinjector at home." He adds that, in addition to convenience, ease of use and cost-effectiveness, subcutaneous amyloid-targeting antibodies may reduce ARIA-E incidence compared with intravenous formulations, as peak drug levels would be lower with the subcutaneous versus the intravenous version.

Could AD be prevented?

As research into slowing AD progression continues, some investigators are turning their attention to stopping the disease before it develops. There are large clinical trials studying whether amyloid-targeting antibodies can prevent AD in people who are at known risk of the disease but who don't yet have cognitive or functional symptoms.

For example, in one AD prevention trial, unimpaired participants ages 55 to 80 with elevated or intermediate levels of amyloid confirmed by brain imaging will receive an amyloid-targeting therapy or placebo to determine if the agent can prevent plaques and tau tangles from developing and thereby prevent AD in older persons at risk of the disease. Study completion is scheduled for 2027.[13]

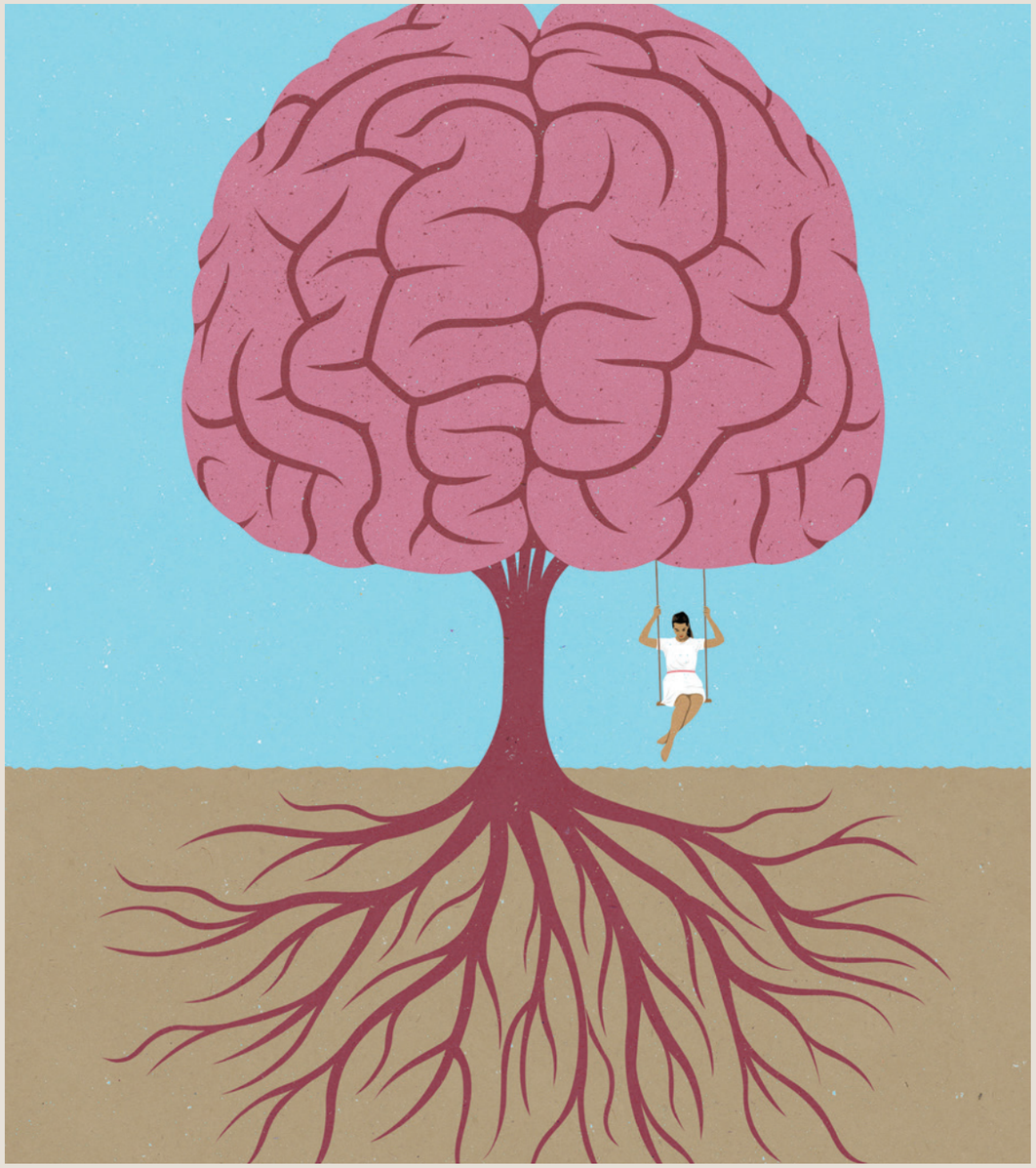

Illustration by John Holcroft / Ikon Images

In another AD intervention trial, unimpaired participants ages 55 to 80 who are at risk of developing AD based on blood biomarkers will receive an amyloid-targeting therapy or placebo to determine if the agent can prevent AD in older persons at risk of the disease. Study completion is also scheduled for 2027.[14]

Although previous AD prevention studies have not yielded clinically meaningful results, Drs. Tariot and Gandy say the concept still is worth exploring given the performance of amyloid-targeting antibodies in removing brain plaques in clinical trials. "Can you stave off the so-called downstream effects on tau and inflammation and membrane function and essentially arrest the disease course?" Dr. Tariot asks. "That's an unknown, but we should soon be getting those answers."

–by Pete Kelly

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Strategies for diagnosing mild cognitive impairment due to AD

Illustration by Stuart Kinlough / Ikon Images

For patients who have Alzheimer's disease (AD), time lost to diagnostic and treatment delays can mean loss of cognitive and everyday functioning. Diagnosing AD in its early stages is critical to forming a management plan that can preserve function for as long as possible and help patients and their loved ones plan for life with the disease.[1]

"The earlier the intervention, the more likely it is to succeed," says Samuel E. Gandy, MD, PhD, Professor of Alzheimer's Disease Research and Associate Director of the Alzheimer's Disease Research Center at Mount Sinai Medical Center in New York City.

Mild cognitive impairment (MCI), an age-related deficit of memory or thinking that does not affect daily functioning, can be the first warning sign that warrants an evaluation to establish whether AD is the cause.[1] And though MCI is mild, it still can be distressing to both patients and their families.

"Often, patients with MCI are painfully aware that something is wrong, but they don't know how to make sense of it," says Pierre N. Tariot, MD, Director of the Banner Alzheimer's Institute in Phoenix and Co-director of the International Alzheimer's Prevention Initiative. "They don't know what's going on. They don't know how serious it is, how much to worry. And their loved ones are worried."

But it can be a challenge to differentiate AD from the myriad other potential causes of MCI—from medical conditions and adverse drug effects to mental illness, vitamin deficiency and more.[2] Constraints on providers' time and an underlying view of MCI symptoms by both patients and providers as a "normal part of aging" also can hinder early AD diagnosis.[1]

Fortunately, the road to identifying AD is becoming clearer, thanks to increased emphasis on the role of biomarkers—in particular amyloid-beta—in AD pathophysiology, combined with advances in detecting amyloid-beta before AD reaches its advanced stages or even develops. "Biomarkers are now essential to AD diagnosis," Dr. Gandy says.

Revised guidelines in development

Researchers have been homing in on the amyloid-beta cascade as a major culprit in AD development, and this hypothesis has paved the way for treatments (see story on p. 2) that have shown efficacy in slowing cognitive and functional decline in AD. It has also fueled a drive toward earlier AD diagnosis by detecting amyloid-beta deposits before they form plaques and, ultimately, the tau tangles associated with AD-related dysfunction.[3]

Because the National Institute on Aging and the Alzheimer's Association recognize the potential biological causes of AD, they are revising criteria for diagnosing and staging the disease based on existence of both biomarkers and cognitive and functional changes. The new recommendations will define AD as a biological disease rather than a clinical syndrome and present the disease course as a clinical continuum that begins with the appearance of biomarkers before AD symptoms surface.[4]

Under the new criteria, AD no longer would be classified as mild, moderate or severe but in stages similar to the staging system used for cancer diagnosis and management. Based on symptoms and level of amyloid-beta proliferation, patients with AD would be staged from 0 (biomarkers portending future AD but currently asymptomatic) to 7 (severe AD symptoms). The system also includes 4 biological stages, from A to D, indicating extent of biomarker proliferation.[5] Currently, the Alzheimer's Association workgroup is revising a draft of the guidelines based on scientific input. For updates, visit *aaic.alz.org/nia-aa.asp*.

> "IT'S IMPORTANT TO IDENTIFY AND EVALUATE A PERSON WITH MILD COGNITIVE IMPAIRMENT AND RENDER AS CLEAR A DIAGNOSIS AS POSSIBLE."
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The diagnostic journey

The road to MCI diagnosis typically begins at the primary care provider's office, when either the patient or family members express concern about

memory loss or "fogginess" or if the provider notices changes such as loss of insight. This is where primary care providers need to start suspecting MCI and its potential causes.[1] "I think it's just a matter of providers having the confidence to do the evaluation a few times and realize that they can go through a relatively simple pathway," Dr. Tariot says (see Figure 1). He and Dr. Gandy describe the steps as follows:

STEP 1

Upon clinical suspicion or patient/family concern, **perform a thorough patient history** to look for past or current illnesses, medications and other risk factors for MCI, Drs. Gandy and Tariot advise. It is critical to have a family member or other knowledgeable caregiver supplement the history, if possible. In addition, **take a detailed family history,** in particular to learn if any relatives had Parkinson's- or AD-related dementia or other forms of dementia.

STEP 2

Next is a **structured neuropsychiatric examination**, during which providers should watch for lapses in cognition during the interview and focus on neurological findings that could suggest an alternative etiology for MCI, such as stroke, Parkinson's disease, vascular dementia or sensory impairment, Dr. Gandy says. Routine lab tests also are necessary.

STEP 3

Equally critical to the examination is **gauging the extent and severity of cognitive impairment**, for which numerous objective assessment tools are available. The Montreal Cognitive Assessment tool (MoCA) is one of the more comprehensive yet easily administered evaluations for assessing cognition, Drs. Gandy and Tariot say. The MoCA assesses a range of cognitive abilities, including orientation, short-term memory, executive function, language, abstraction, attention, naming and spatial relations.

A MoCA score between 18 and 25 typically suggests MCI, with lower scores indicating more severe impairment. However, any score of 21 or lower should be concerning, Dr. Gandy says.

For assessing function, the AD8 or Functional Assessment Questionnaire (FAQ) is an effective tool, Dr. Tariot says. Either assessment can be administered in a busy primary care setting in 10 minutes or less.

STEP 4

Then, **routine structural brain imaging** with unenhanced magnetic resonance imaging (MRI) or, if MRI is contraindicated, computerized tomography (CT) is required to assess for structural or other neurological abnormalities.

STEP 5

Next, **rule out other causes**. "The next step then is to understand what we'd be looking for and to consider what sorts of culprits can cause mild cogni-

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Figure 1.

Steps for diagnosing mild cognitive impairment (MCI) due to Alzheimer's disease[1,2]

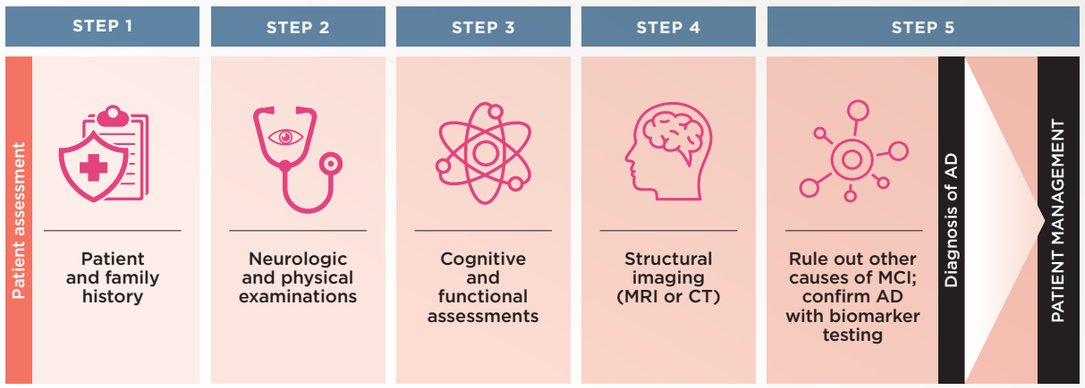

Illustration by Stuart Kinlough / Ikon Images

> "BIOMARKERS ARE NOW ESSENTIAL TO AD DIAGNOSIS."
>
> —Samuel E. Gandy, MD, PhD

tive impairment and need to be ruled out," Dr. Tariot says. While many cases are due to slowly emerging AD,[1] he adds that other identifiable and reversible or more treatable conditions could instead be to blame. These include brain trauma, infection, mental illness (e.g., anxiety, depression), metabolic dysfunction (e.g., type 2 diabetes, hypothyroidism), neurologic disorder (e.g., vascular dementia) and toxin exposure.

Finally, **confirm with biomarker testing.** If AD is suspected after all other causes have been ruled out, an amyloid positron-emission tomography (PET) scan or cerebrospinal fluid (CSF) testing can confirm the existence of amyloid-beta brain deposits and confirm the AD diagnosis. While Drs. Gandy and Tariot say either test modality is effective, they note that CSF testing is slightly more sensitive. "You pick up around 10% more patients with subtle elevated brain amyloid that you might miss with an amyloid PET scan," says Dr. Tariot, adding that CSF testing also measures existence of tau proteins, another marker that can help establish AD pathology. Also consider CSF testing when clinical features such as amnesia or hallucinations might point to specific diagnoses, notes Dr. Gandy.

However, third-party payers often dictate the choice of testing modality, and scanning with amyloid PET, which entails use of specific radiotracers sensitive to amyloid proteins, has shown effectiveness in detecting brain amyloid plaques indicative of early- or later-stage AD. In one study that followed 11,409 patients with MCI or dementia, amyloid PET scans were instrumental in ruling out AD in patients misdiagnosed with the disease and in diagnosing AD among patients in whom the disease had been missed.[6]

Blood-based biomarker testing (BBBM) is under investigation as a testing option for amyloid-beta presence. Data are insufficient to support widespread use of BBBM as a standalone AD screening test[7] but could be used to confirm the need for CSF testing or amyloid PET scan. "If the blood test is definitively negative, we're done for now," Dr. Tariot says. "If it's positive, let's confirm that result with a spinal test or a PET scan."

When the diagnosis is MCI due to AD: next steps

If amyloid PET or CSF testing indicates AD, it's time to discuss disease management options. The discussion should start with a review of how to cope day-to-day with MCI, then move to the potential benefits and risks of available treatments, say Drs. Gandy and Tariot, in particular the newer amyloid-targeting antibodies that have shown efficacy in destroying brain amyloid plaques and slowing cognitive and functional decline. Most importantly, now that early-stage AD has been diagnosed, both the patient and their family can be armed with information to help maximize their future quality of life.

"If I were a patient, I'd have a better idea of what lies ahead," Dr. Tariot says. "I can tell my loved ones and doctors how I want my future care plan to be if I deteriorate. My loved ones and I can be counseled as to what I'm living through now, how to cope with it better, how to mitigate things in a practical day-to-day sense, how to communicate a little differently…it's important to identify and evaluate a person with mild cognitive impairment and render as clear a diagnosis as possible." ●

—by Pete Kelly

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LEQEMBI® (lecanemab-irmb) injection, for intravenous use. Rx Only.

The following is a Brief Summary; refer to full Prescribing Information for complete product information.

WARNING: AMYLOID RELATED IMAGING ABNORMALITIES

Monoclonal antibodies directed against aggregated forms of beta amyloid, including LEQEMBI, can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). Incidence and timing of ARIA vary among treatments. ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events rarely can occur. Serious intracerebral hemorrhages, some of which have been fatal, have been observed in patients treated with this class of medications *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*.

ApoE ε4 Homozygotes

Patients who are apolipoprotein E ε4 (ApoE ε4) homozygotes (approximately 15% of Alzheimer's disease patients) treated with this class of medications, including LEQEMBI, have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. Prescribers should inform patients that if genotype testing is not performed they can still be treated with LEQEMBI; however, it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA *[see Warnings and Precautions (5.1)]*.

Consider the benefit of LEQEMBI for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with LEQEMBI *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

LEQEMBI is indicated for the treatment of Alzheimer's disease. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Confirm the presence of amyloid beta pathology prior to initiating treatment

2.2 Dosing Instructions

The recommended dosage of LEQEMBI is 10 mg/kg that must be diluted then administered as an intravenous infusion over approximately one hour, once every two weeks.

If an infusion is missed, administer the next dose as soon as possible.

2.3 Monitoring and Dosing Interruption for Amyloid Related Imaging Abnormalities

LEQEMBI can cause amyloid related imaging abnormalities-edema (ARIA-E) and -hemosiderin deposition (ARIA-H) *[see Warnings and Precautions (5.1)]*.

Monitoring for ARIA

Obtain a recent baseline brain magnetic resonance imaging (MRI) prior to initiating treatment with LEQEMBI. Obtain an MRI prior to the 5th, 7th, and 14th infusions. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including an MRI if indicated.

Recommendations for Dosing Interruptions in Patients with ARIA

ARIA-E

The recommendations for dosing interruptions for patients with ARIA-E are provided in Table 1.

Table 1: Dosing Recommendations for Patients with ARIA-E

Clinical Symptom Severity[1]	ARIA-E Severity on MRI[2]		
	Mild	Moderate	Severe
Asymptomatic	May continue dosing	Suspend dosing[3]	Suspend dosing[3]
Mild	May continue dosing based on clinical judgment	Suspend dosing[3]	
Moderate or Severe	Suspend dosing[3]		

[1]Clinical Symptom Severity Categories:
Mild: discomfort noticed, but no disruption of normal daily activity.
Moderate: discomfort sufficient to reduce or affect normal daily activity.
Severe: incapacitating, with inability to work or to perform normal daily activity.

[2]See Table 3 for MRI severity *[Warnings and Precautions (5.1)]*.

[3]Suspend until MRI demonstrates radiographic resolution and symptoms, if present, resolve; consider a follow-up MRI to assess for resolution 2 to 4 months after initial identification. Resumption of dosing should be guided by clinical judgment

ARIA-H

The recommendations for dosing interruptions for patients with ARIA-H are provided in Table 2.

Table 2: Dosing Recommendations for Patients with ARIA-H

Clinical Symptom Severity	ARIA-H Severity on MRI[1]		
	Mild	Moderate	Severe
Asymptomatic	May continue dosing	Suspend dosing[2]	Suspend dosing[3]
Symptomatic	Suspend dosing[2]	Suspend dosing[2]	

[1]See Table 3 for MRI severity *[Warnings and Precautions (5.1)]*.

[2]Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; resumption of dosing should be guided by clinical judgment; consider a follow-up MRI to assess for stabilization 2 to 4 months after initial identification.

[3]Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; use clinical judgment in considering whether to continue treatment or permanently discontinue LEQEMBI.

In patients who develop intracerebral hemorrhage greater than 1 cm in diameter during treatment with LEQEMBI, suspend dosing until MRI demonstrates radiographic stabilization and symptoms, if present, resolve. Use clinical judgment in considering whether to continue treatment after radiographic stabilization and resolution of symptoms or permanently discontinue LEQEMBI.

3 DOSAGE FORMS AND STRENGTHS

LEQEMBI is a clear to opalescent and colorless to pale yellow solution, available as:

- Injection: 500 mg/5 mL (100 mg/mL) in a single-dose vial
- Injection: 200 mg/2 mL (100 mg/mL) in a single-dose vial

4 CONTRAINDICATIONS

LEQEMBI is contraindicated in patients with serious hypersensitivity to lecanemab-irmb or to any of the excipients of LEQEMBI. Reactions have included angioedema and anaphylaxis *[see Warnings and Precautions (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Amyloid Related Imaging Abnormalities

Monoclonal antibodies directed against aggregated forms of beta amyloid, including LEQEMBI, can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, and ARIA with hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis. ARIA can occur spontaneously in patients with Alzheimer's disease. ARIA-H associated with monoclonal antibodies directed against aggregated forms of beta amyloid generally occurs in association with an occurrence of ARIA-E. ARIA-H of any cause and ARIA-E can occur together.

ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. When present, reported symptoms associated with ARIA may include headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur. Symptoms associated with ARIA usually resolve over time. The risk of ARIA, including symptomatic and serious ARIA, is increased in apolipoprotein E ε4 (ApoE ε4) homozygotes. In addition to ARIA, intracerebral hemorrhages greater than 1 cm in diameter have occurred in patients treated with LEQEMBI.

Consider the benefit of LEQEMBI for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with LEQEMBI.

Incidence of ARIA

Symptomatic ARIA occurred in 3% (29/898) of patients treated with LEQEMBI in Study 2. Serious symptoms associated with ARIA were reported in 0.7% (6/898) of patients treated with LEQEMBI. Clinical symptoms associated with ARIA resolved in 79% (23/29) of patients during the period of observation. Similar findings were observed in Study 1.

Including asymptomatic radiographic events, ARIA was observed in 21% (191/898) of patients treated with LEQEMBI, compared to 9% (84/897) of patients on placebo in Study 2.

ARIA-E was observed in 13% (113/898) of patients treated with LEQEMBI compared with 2% (15/897) of patients on placebo. ARIA-H was observed in 17% (152/898) of patients treated with LEQEMBI compared with 9% (80/897) of patients on placebo. There was no increase in isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) for LEQEMBI compared to placebo.

ApoE ε4 Carrier Status and Risk of ARIA

Approximately 15% of Alzheimer's disease patients are ApoE ε4 homozygotes. In Study 2, 16% (141/898) of patients in the LEQEMBI arm were ApoE ε4 homozygotes, 53% (479/898) were heterozygotes, and 31% (278/898) were noncarriers. The incidence of ARIA was higher in ApoE ε4 homozygotes (45% on LEQEMBI vs. 22% on placebo) than in heterozygotes (19% on LEQEMBI vs 9% on placebo) and noncarriers (13% on LEQEMBI vs 4% on placebo). Among patients treated with LEQEMBI, symptomatic ARIA-E occurred in 9% of ApoE ε4 homozygotes compared with 2% of heterozygotes and 1% noncarriers. Serious events of ARIA occurred in 3% of ApoE ε4 homozygotes, and approximately 1% of heterozygotes and noncarriers. The recommendations on management of ARIA do not differ between ApoE ε4 carriers and noncarriers *[see Dosage and Administration (2.3)]*. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. Prescribers should inform patients that if genotype testing is not performed they can still be treated with LEQEMBI; however, it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA. An FDA-authorized test for the detection of ApoE ε4 alleles to identify patients at risk of ARIA if treated with LEQEMBI is not currently available. Currently available tests used to identify ApoE ε4 alleles may vary in accuracy and design.

Radiographic Findings

The radiographic severity of ARIA associated with LEQEMBI was classified by the criteria shown in Table 3.

Table 3: ARIA MRI Classification Criteria

ARIA Type	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity confined to sulcus and/or cortex/ subcortex white matter in one location <5 cm	FLAIR hyperintensity 5 to 10 cm in single greatest dimension, or more than 1 site of involvement, each measuring <10 cm	FLAIR hyperintensity >10 cm with associated gyral swelling and sulcal effacement. One or more separate/ independent sites of involvement may be noted
ARIA-H microhemorrhage	≤ 4 new incident microhemorrhages	5 to 9 new incident microhemorrhages	10 or more new incident microhemorrhages
ARIA-H superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	>2 areas of superficial siderosis

The majority of ARIA-E radiographic events occurred early in treatment (within the first 7 doses), although ARIA can occur at any time and patients can have more than 1 episode. The maximum radiographic severity of ARIA-E in patients treated with LEQEMBI was mild in 4% (37/898) of patients, moderate in 7% (66/898) of patients, and severe in 1% (9/898) of patients. Resolution on MRI occurred in 52% of ARIA-E patients by 12 weeks, 81% by 17 weeks, and 100% overall after detection. The maximum radiographic severity of ARIA-H microhemorrhage in patients treated with LEQEMBI was mild in 9% (79/898), moderate in 2% (19/898), and severe in 3% (28/898) of patients; superficial siderosis was mild in 4% (38/898), moderate in 1% (8/898), and severe in 0.4% (4/898). Among patients treated with LEQEMBI, the rate of severe radiographic ARIA-E was highest in ApoE ε4 homozygotes 5% (7/141), compared to heterozygotes 0.4% (2/479) or noncarriers 0% (0/278). Among patients treated with LEQEMBI, the rate of severe radiographic ARIA-H was highest in ApoE ε4 homozygotes 13.5% (19/141), compared to heterozygotes 2.1% (10/479) or noncarriers 1.1% (3/278).

Intracerebral Hemorrhage

Intracerebral hemorrhage greater than 1 cm in diameter was reported in 0.7% (6/898) of patients in Study 2 after treatment with LEQEMBI compared to 0.1% (1/897) on placebo. Fatal events of intracerebral hemorrhage in patients taking LEQEMBI have been observed.

Concomitant Antithrombotic Medication

In Study 2, baseline use of antithrombotic medication (aspirin, other antiplatelets, or anticoagulants) was allowed if the patient was on a stable dose. The majority of exposures to antithrombotic medications were to aspirin. Antithrombotic medications did not increase the risk of ARIA with LEQEMBI. The incidence of intracerebral hemorrhage was 0.9% (3/328 patients) in patients taking LEQEMBI with a concomitant antithrombotic medication at the time of the event compared to 0.6% (3/545 patients) in those who did not receive an antithrombotic. Patients taking LEQEMBI with an anticoagulant alone or combined with an antiplatelet medication or aspirin had an incidence of intracerebral hemorrhage of 2.5% (2/79 patients) compared to none in patients who received placebo.

Because intracerebral hemorrhages greater than 1 cm in diameter have been observed in patients taking LEQEMBI, additional caution should be exercised when considering the administration of anticoagulants or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with LEQEMBI.

Other Risk Factors for Intracerebral Hemorrhage

Patients were excluded from enrollment in Study 2 for findings on neuroimaging that indicated an increased risk for intracerebral hemorrhage. These included findings suggestive of cerebral amyloid angiopathy (prior cerebral hemorrhage greater than 1 cm in greatest diameter, more than 4 microhemorrhages, superficial siderosis, vasogenic edema) or other lesions (aneurysm, vascular malformation) that could potentially increase the risk of intracerebral hemorrhage.

The presence of an ApoE ε4 allele is also associated with cerebral amyloid angiopathy, which has an increased risk for intracerebral hemorrhage.

Caution should be exercised when considering the use of LEQEMBI in patients with factors that indicate an increased risk for intracerebral hemorrhage and in particular for patients who need to be on anticoagulant therapy.

Monitoring and Dose Management Guidelines

Recommendations for dosing in patients with ARIA-E depend on clinical symptoms and radiographic severity *[see Dosage and Administration (2.3)]*. Recommendations for dosing in patients with ARIA-H depend on the type of ARIA-H and radiographic severity *[see Dosage and Administration (2.3)]*. Use clinical judgment in considering whether to continue dosing in patients with recurrent ARIA-E.

Baseline brain MRI and periodic monitoring with MRI are recommended *[see Dosage and Administration (2.3)]*. Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment with LEQEMBI. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI if indicated. If ARIA is observed on MRI, careful clinical evaluation should be performed prior to continuing treatment.

There is no experience in patients who continued dosing through symptomatic ARIA-E, or through asymptomatic but radiographically severe ARIA-E. There is limited experience in patients who continued dosing through asymptomatic but radiographically mild to moderate ARIA-E. There are limited data in dosing patients who experienced recurrent ARIA-E.

The Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) is a voluntary provider-enrolled patient registry that collects information on treatments for Alzheimer's disease, including LEQEMBI. Providers may obtain information about the registry at www.alz-net.org or contact alz-net@acr.org.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions, including angioedema, bronchospasm, and anaphylaxis, have occurred in patients who were treated with LEQEMBI. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction, and initiate appropriate therapy. LEQEMBI is contraindicated in patients with a history of serious hypersensitivity to lecanemab-irmb or to any of the excipients of LEQEMBI.

5.3 Infusion-Related Reactions

In Study 2, infusion-related reactions were observed in 26% (237/898) of patients treated with LEQEMBI compared to 7% (66/897) of patients on placebo; and the majority (75%, 178/237) occurred with the first infusion. Infusion-related reactions were mostly mild (69%) or moderate (28%) in severity. Infusion-related reactions resulted in discontinuations in 1% (12/898) of patients treated with LEQEMBI. Symptoms of infusion-related reactions include fever and flu-like symptoms (chills, generalized aches, feeling shaky, and joint pain), nausea, vomiting, hypotension, hypertension, and oxygen desaturation.

After the first infusion in Study 1, 38% of patients treated with LEQEMBI had transient decreased lymphocyte counts to less than 0.9 $x10^9$/L compared to 2% in patients on placebo, and 22% of patients treated with LEQEMBI had transient increased neutrophil counts to greater than 7.9 $x10^9$/L compared to 1% of patients on placebo. Lymphocyte and neutrophil counts were not obtained after the first infusion in Study 2.

In the event of an infusion-related reaction, the infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy initiated as clinically indicated. Prophylactic treatment with antihistamines, acetaminophen, nonsteroidal anti-inflammatory drugs, or corticosteroids prior to future infusions may be considered.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Amyloid Related Imaging Abnormalities *[see Warnings and Precautions (5.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of LEQEMBI has been evaluated in 2090 patients who received at least one dose of LEQEMBI. In Studies 1 and 2 in patients with Alzheimer's disease, 1059 patients received LEQEMBI 10 mg/kg every two weeks. Of these 1059 patients, 50% were female, 79% were White, 15% were Asian, 12% were of Hispanic or Latino ethnicity, and 2% were Black. The mean age at study entry was 72 years (range from 50 to 90 years).

In the combined double-blind, placebo-controlled period and long-term extension period of Studies 1 and 2, 1604 patients received LEQEMBI for at least 6 months, 1261 patients for at least 12 months, and 965 patients for 18 months.

In the double-blind, placebo-controlled period in Study 2, patients stopped study treatment because of an adverse reaction in 7% of patients treated with LEQEMBI, compared to 3% of patients on placebo.

In Study 2, the most common adverse reaction leading to discontinuation of LEQEMBI was ARIA-H microhemorrhages that led to discontinuation in 2% (15/898) of patients treated with LEQEMBI compared to <1% (1/897) of patients on placebo. Adverse reactions reported in Study 2 are shown in Table 4.

Table 4: Adverse Reactions Reported in at Least 5% of Patients Treated With LEQEMBI 10 mg/kg Every Two Weeks and at Least 2% Higher than Placebo in Study 2

Adverse Reaction	LEQEMBI N=898 %	Placebo N=897 %
Infusion-related reactions	26	7
ARIA-H	14	8
ARIA-E	13	2
Headache	11	8
Superficial siderosis of central nervous system	6	3
Rash[1]	6	4
Nausea/Vomiting	6	4

[1]Rash includes acne, erythema, infusion site rash, injection site rash, rash, rash erythematous, rash pruritic, skin reactions, and urticaria.

Less Common Adverse Reactions

Atrial fibrillation occurred in 3% of patients treated with LEQEMBI compared to 2% in patients on placebo. In Study 1, lymphopenia or decreased lymphocyte count were reported in 4% of patients treated with LEQEMBI after the first dose, compared to less than 1% of patients on placebo *[see Warnings and Precautions (5.3)]*; lymphocytes were not measured after the first dose in Study 2.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on LEQEMBI use in pregnant women to evaluate for a drug associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. No animal studies have been conducted to assess the potential reproductive or developmental toxicity of LEQEMBI.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

8.2 Lactation

Risk Summary

There are no data on the presence of lecanemab-irmb in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Published data from other monoclonal antibodies generally indicate low passage of monoclonal antibodies into human milk and limited systemic exposure in the breastfed infant. The effects of this limited exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LEQEMBI and any potential adverse effects on the breastfed infant from LEQEMBI or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of LEQEMBI in pediatric patients have not been established.

8.5 Geriatric Use

In Studies 1 and 2, the age of patients exposed to LEQEMBI 10 mg/kg every two weeks (n=1059) ranged from 50 to 90 years, with a mean age of 72 years; 81% were 65 years and older, and 39% were 75 years and older. No overall differences in safety or effectiveness of LEQEMBI have been observed between patients 65 years of age and older and younger adult patients.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide).

Amyloid Related Imaging Abnormalities

Inform patients that LEQEMBI may cause Amyloid Related Imaging Abnormalities or "ARIA". ARIA most commonly presents as a temporary swelling in areas of the brain that usually resolves over time. Some people may also have small spots of bleeding in or on the surface of the brain. Inform patients that most people with swelling in areas of the brain do not experience symptoms, however, some people may experience symptoms such as headache, confusion, dizziness, vision changes, nausea, aphasia, weakness, or seizure. Instruct patients to notify their healthcare provider if these symptoms occur. Inform patients that events of intracerebral hemorrhage greater than 1 cm in diameter have been reported infrequently in patients taking LEQEMBI, and that the use of anticoagulant or thrombolytic medications while taking LEQEMBI may increase the risk of bleeding in the brain. Notify patients that their healthcare provider will perform MRI scans to monitor for ARIA *[see Warnings and Precautions (5.1)]*.

Inform patients that although ARIA can occur in any patient treated with LEQEMBI, there is an increased risk in patients who are ApoE ε4 homozygotes and that testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. Inform patients that if testing is not performed, it cannot be determined if they are ApoE ε4 homozygotes and at a higher risk for ARIA.

Patient Registry

Advise patients that the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) is a voluntary provider-enrolled patient registry that collects information on treatments for Alzheimer's disease, including LEQEMBI. Encourage patients to participate in the ALZ-NET registry *[see Warnings and Precautions (5.1)]*.

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions, including angioedema and anaphylaxis have occurred in patients who were treated with LEQEMBI. Advise patients to seek immediate medical attention if they experience any symptoms of serious or severe hypersensitivity reactions *[see Warnings and Precautions (5.2)]*.

Infusion-Related Reactions

Advise patients of the potential risk of infusion-related reactions, which can include flu-like symptoms, nausea, vomiting, and changes in blood pressure, the majority of which occur with the first infusion *[see Warnings and Precautions (5.3)]*.

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Helping patients and care partners cope with a diagnosis of early AD

Meeting the patient and their care partners where they are during the initial period of acceptance and planning that follows diagnosis can have a significant impact.

Receiving a diagnosis of Alzheimer's disease (AD) or mild cognitive impairment (MCI) due to AD comes with a devastating emotional impact. According to the Alzheimer's Research Association, when a person hears the news early in their journey, they become aware of their impending decline, and they may experience grief, anger, loss, fear, shock, disbelief and more.[1-3]

And while the patient is dealing with these complex emotions, so too are their care partners, the preferred term at this stage, notes Valerie T. Cotter, DrNP, AGPCNP-BC, FAANP, FAAN, "especially in MCI due to early AD when the person doesn't need a caregiver but someone who will partner with them," says Cotter, who is Associate Professor at Johns Hopkins School of Nursing and School of Medicine in the Department of Psychiatry & Behavioral Sciences and a nurse practitioner in the Memory and Alzheimer's Treatment Center. In addition to facing years of providing support in a way they might never have anticipated, care partners must also process the fact that the affected person will likely lose their memories of them while also experiencing personality changes that may render them unrecognizable.

Adding to the challenge is that AD may impair the person's ability to process emotions, according to some experts, making it tougher for care partners to know how to provide the best support.[2]

However, as a clinician, you have the opportunity to make a positive impact on the patient's care by providing support through this period of acceptance and planning.

"I think it's really important that the clinician not only think about pharmacologic interventions but especially think about psychosocial interventions," says Cotter. In her practice, Cotter has found several strategies that can help ease the transition for patients and care partners. Here, she offers insight on how to provide psychosocial support.

Make it a team effort

It's crucial for anyone with a cognitive impairment diagnosis to have care partners at home who can not only support them through their diagnosis but also in their day-to-day lives as their capabilities shift. "Our schedulers encourage new patients to come in to the office with what we call a 'knowledgeable informant,' whether an adult child or a spouse or friend," explains Cotter. If they don't have anyone who can make it, she says, "I always ask them, 'Who else can I talk with on the phone after the appointment to learn more about you and how you're doing?'"

That knowledgeable informant will then become an ongoing partner in their care. And in the early stages, it's just as important to keep that person informed as the patient so they know what's ahead. When people don't have someone to call on or live far away from loved

ones, Cotter points them to a Geriatric Care Manager, a nurse or social worker who can help identify needs and identify solutions to meet them.

As for providing background and education to get them started down the path to understanding what's ahead, if a practice doesn't already have pamphlets with the basics and where to get more support and information, Cotter recommends both patients and their care partners turn to the Alzheimer's Association for education, support and to connect with other families in their circumstances.

Reframe the discussion

The burdens that come along with this diagnosis can be substantial, but Cotter says reframing how you talk about it to focus on their future care can have a positive impact. "I try to help people understand that even though it is a devastating diagnosis, there's always hope around having a good quality of life for a long time because people can live for years with Alzheimer's disease."

While she can't promise it will be easy, she also emphasizes that there can still be enjoyment. When it comes to planning, she says, "We're going to do the best we can to help maintain your function and quality of life through these stages." She finds this reframing helps both patients and the people around them feel less helpless when they're coming to terms with the challenges they'll be facing.

> "DEVELOPING A ROUTINE WHERE THERE'S DAYTIME ACTIVITY WITH PHYSICAL, SOCIAL AND MENTAL STIMULATION DURING THE DAY AND THEN AN ADEQUATE 6 TO 8 HOURS OF SLEEP EVERY NIGHT IS KEY."
>
> —Valerie T. Cotter, DrNP, AGPCNP-BC, FAANP, FAAN

Encourage "planning while you can"

Cotter says processing a future of reduced function can be especially tough. "Everyone wants to maintain the level of independence that they've always had," she says. But when it comes to big and little to-dos like household chores, cooking, grocery shopping, etc., "in the early stages, the patient and their care partner really need to think about how that's going to change and who will get those things done." She also says having a driving evaluation in the early stages is important. "You don't want to wait until there's a problem with them getting lost or having an accident before it's recognized," she warns.

And on a larger scale, she explains, "It's crucial to discuss financial implications, power of attorney and advance directives." She says she tells her patients they need to consider, "Who's going to help me with those things when my disease progresses and I can no longer do them by myself?" while they are still able to understand the impact and help get rid of the unknowns.

While this is important for logistical reasons, it's equally important to help soothe the anxiety around the what-ifs—not only for the patient but also for their support system. Cotter says participating in the planning stage can help make all parties involved feel a bit more in control and ready for what's to come.

Promote stimulating activities

While having a daily routine can be helpful in getting patients with impaired memory through each day smoothly, Cotter is adamant about making sure patients have stimulation in their lives. She says patients dealing with dementia "can get really bored, and because they lack the initiative or motivation or organization, they sit in front of the TV all day long—that's not good." She continues, "So developing a routine where there's daytime activity with physical, social and mental stimulation during the day and then an adequate 6 to 8 hours of sleep every night is key."

One thing she finds to be helpful: Adult day programs, community-based programs where patients go a few times a week. They have professional staff there with nurses and social workers, and they do a full assessment of the patient and help engage them in activities that fit their capabilities and interests."

Providing stimulation is not merely a way to help people with dementia pass the time in more engaging ways: According to research published in Germany, psychosocial interventions can have a positive impact. For example, cognitive stimulation and cognitive training improve cognitive abilities, activity planning and reminiscence can enhance emotional well-being, and aromatherapy and music therapy can reduce behavioral symptoms. Art programs have also been shown to improve quality of life and feelings of well-being.[4-6]

Meet them where they are

Denial is commonly reported in the newly diagnosed, according to the Alzheimer's Association. Nonetheless, Cotter finds that with cognitive decline it's important not to force anything but rather meet the patient where they are. She says when family members talk of seeing denial in the patient, there may be something else at play. "My experience has told me that the family sees it as an active form of denial, when really it may be a decreased capacity to process and understand their condition."

Her strategy in this situation? While she goes over the information about their diagnosis at the first encounter, if the patient doesn't seem to be grasping it at future visits, she turns the focus to what they may be experiencing instead. "It's a lot more palatable to describe their condition related to symptoms. They may have trouble with words and there's stigma with the diagnosis—it can cause anxiety and agitation if you keep pushing it," she says. "You have to follow the lead of the person who is experiencing it and how much they are going to be able to remember what you tell them."

Denial on the part of care partners is much more worrisome, says Cotter, as they'll need to understand the importance of their role in keeping their loved one safe. In that case, she spends more time educating them, listening to their concerns and—most importantly—pointing them toward support. ●

—by Beth Shapouri

STRATEGIES FOR CARE PARTNERS AS THEIR LOVED ONE'S DISEASE PROGRESSES[6,7]

Family members and care partners will need guidance to help them adjust to their loved one's diagnosis and the changes ahead. First, it is crucial to provide them with the name and contact information for a social worker who can answer questions and offer resources throughout their journey. And while care partners can understandably be overwhelmed by increasing responsibilities, these everyday strategies may ease some of the burden:

- Keep things simple. Focus on communicating one thing at a time.
- Encourage a daily routine so the person knows when and how certain things will happen.
- Reassure the person that they are safe and you are there to help.
- Focus on their feelings. For example, say, "You seem worried."
- Don't argue with the person or show your frustration or anger.
- Use humor when you can.
- Take the person for a walk or find them a safe place to walk if they are restless or tend to pace.

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PATIENT: MARTIN, 69, HAD A HISTORY OF EARLY ALZHEIMER'S DISEASE (AD) AND MILD HYPERTENSION.

"Martin's scans confirmed a slowing of his early AD"

PHYSICIAN:
Anne-Marie Osibajo, MD

Behavioral neurologist and neuropsychiatrist, Icahn School of Medicine at Mount Sinai in New York City

Treatment history:
About 5 years ago, when he was 64, Martin's family noticed that he kept repeating questions and forgetting basic things, like what they had for dinner or the date and time of his grandson's soccer game. This was highly unusual for someone who had been an investment banker. In fact, as Martin's forgetfulness worsened, he was asked to resign from his position because he had been making a series of mistakes, such as failing to execute trades or provide his clients with important paperwork.

When I first saw Martin more than a year ago, his wife told me he was constantly misplacing his wallet and glasses, to the point where he would stick multiple written reminders around the house, on countertops, doors and windows—even in the refrigerator. When that didn't work, he became increasingly frustrated, anxious and, occasionally, depressed. Tasks and activities that he used to enjoy, such as planning family vacations, were nearly impossible to complete.

Initiating treatment:
Given his symptoms and his age, Martin was a good candidate for a novel therapy being studied in clinical trials, an injectable drug that targets the harmful buildup of beta-amyloid plaques in the brain. Martin's eligibility for the drug was confirmed by his Montreal Cognitive Assessment score of 22, and by the presence of mild amyloid plaques on an amyloid PET scan, which is indicative of mild cognitive impairment (MCI) due to AD. Conditions like Lewy body disease, frontotemporal dementia or Parkinson's disease were ruled out.

Martin was initially hesitant to receive an infusion, but when I discussed the potential benefits of anti-amyloid therapies—most notably that it might delay the progression of his early AD—he agreed to try it. Side effects are usually mild and include headaches, dizziness and fever, but they generally pass within a few weeks. We also discussed possible major adverse effects, notably amyloid-related imaging abnormalities (ARIA), often marked by edema or hemorrhage (for more on ARIA, see p. 5). As for Martin, he had no major complaints about the biweekly infusions. He also received sertraline to treat his anxiety and depression.

More than a year later, two follow-up MRIs 6 months apart have confirmed that there were no significant changes in brain size, and amyloid PET scan revealed that the amount of amyloid plaques in Martin's brain had not increased. Not only has the progression of his early AD slowed, but—even though he still has memory challenges—the impairment has not worsened. And while Martin never returned to work, he's doing some consulting for his son-in-law's accounting firm, which has boosted his self-esteem and greatly lessened his anxiety.

Considerations:
Anti-amyloid therapies are disease-modifying agents that are currently approved for MCI due to AD and mild AD dementia. Studies have shown they slow progression of the disease by 5 or 6 months in most patients and possibly even longer in Martin's case. Gaining back that time was especially important for Martin because he had always intended to travel in retirement and spend more time with his grandkids.

Like Martin, your patients with memory impairment independent of normal aging or a heart condition, as well as their families, will likely want to maximize the time they have before AD seriously interferes with their functioning. For people like Martin who are otherwise in good health, anti-amyloid agents offer a clinically meaningful path toward making those precious moments possible.

NEW!
KOL ON DEMAND VIDEO
Scan here for more insight on Martin's case.

Illustration by Juhee Kim

Q

A

Expert insight on managing Alzheimer's disease

Getting to the bottom of MCI

Q: When you suspect a patient has mild cognitive impairment, how do you confirm the diagnosis and potential cause?

A: Mild cognitive impairment (MCI) is characterized by subtle changes in memory and thinking serious enough to be noticed by the affected person and their close family and friends but not severe enough to disrupt their ability to carry out everyday activities. MCI is often mistakenly accepted as a "normal" part of aging, yet it is not normal or even typical. In fact, it's estimated that 12% to 18% of people age 60 or older have MCI. While some individuals with MCI revert to normal cognition or remain stable, studies suggest 10% to 15% of individuals with MCI go on to develop dementia each year. About one-third of people with MCI due to Alzheimer's disease will develop clinical dementia within 5 years.

Although a physician may suspect MCI because of patient-reported symptoms, no test can provide a definitive diagnosis. So doctors must rely on other means, such as a review of the patient's medical history, patient questionnaires, clinical exams and brief assessments to evaluate memory and thinking. Things they should look for include changes in reasoning, problem-solving, planning, naming and comprehension.

Sometimes, an MCI diagnosis requires ruling out other systemic or brain diseases, such as Parkinson's disease, dementia with Lewy bodies (associated with rapid eye movement sleep abnormalities), cerebrovascular disease in the blood vessels that support the brain, prion disease or cancer (characterized by a more rapid cognitive decline).

For MCI due to Alzheimer's, guidelines recommend finding biomarkers (e.g., amyloid-beta, tau) that indicate changes in the brain, cerebrospinal fluid and/or blood and that are associated with Alzheimer's disease pathology.

Illustration by Juhee Kim

Benefits of early diagnosis

Q: Why is it critical to detect Alzheimer's disease early and how would you confirm the diagnosis?

A: Early detection and diagnosis of Alzheimer's disease (AD) and other dementias is critical because it offers the best opportunity for patient care, management and treatment. It also provides diagnosed individuals and their family members more time to plan for the future, adopt lifestyle changes that may help slow disease progression, participate in clinical trials and enjoy a higher quality of life for as long as possible.

It also gives diagnosed people the opportunity to express their wishes about legal, financial and end-of-life care decisions as well as to address potential safety issues, such as driving or wandering, before a crisis occurs.

While there is still no cure for AD, the advent of new FDA-approved treatments proven to delay progression drives home the importance of early detection and diagnosis. The reason: They are only available to individuals in the earliest stages of the disease. What's more, as therapies continue to be developed, early and accurate diagnosis will help determine eligibility for current as well as future treatments.

To confirm a diagnosis of AD, clinicians can collect cerebrospinal fluid (CSF) via a spinal tap or perform special PET scans to detect amyloid-beta and tau in the brain, two hallmarks of Alzheimer's disease. Less expensive and less invasive blood tests are in development but are not yet ready or approved for clinical use.

Looking for changes

Q: For patients with early- to mid-stage AD, what type of personality changes are common?

A: Depression is common among people in the early and middle stages of AD. It can be triggered by the trauma of receiving a fatal disease diagnosis, recognition that one's memory and thinking are declining, loss of independence or feelings of guilt that the person is or will become a burden to their family.

However, identifying depression in someone with AD can be difficult as it shares some of the same symptoms as dementia, including apathy, loss of interest in activities and hobbies, social withdrawal, trouble concentrating and impaired thinking. Prompt diagnosis is crucial, as treatment can improve the person's sense of well-being and function. Medications or lifestyle changes, such as exercise, improving diet and sleep, and increasing social activity, are common treatments.

As AD progresses, a person may exhibit behaviors such as anxiety, agitation and, in some cases, aggression. It is important to alert the person's family members that these behaviors are not intentional; they are disease-related.

The key during any stage of AD is to meet people where they are. The disease affects individuals differently. The goal should always be to provide "person-centered" care that is grounded in knowing the person. Knowing a person's likes, dislikes and preferences can help providers and caregivers better understand what is triggering the behavior so they can take steps to address it in a way that is responsive to the individual.

OUR EXPERT
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EXAM TOOL

Detecting signs of mild cognitive impairment

Diagnosing mild cognitive impairment (MCI) is critical not only for establishing possible causes, including early-stage Alzheimer's disease, but also for creating a management plan that preserves the patient's functioning for as long as possible. Often, the first signs are detected when a patient or a family member expresses concern about memory loss or problems with daily activities. When this occurs, consider using the questionnaire below as a first step. If their answers indicate cognitive decline, further assessment is needed and, if warranted, an amyloid PET scan or CSF testing (see page 8 for more on diagnosing MCI).

ASK THE PATIENT AND/OR FAMILY MEMBER THE FOLLOWING:

Compared with how you (or your loved one) were 10 years ago, have you observed changes in any of the following situations?

SCORE *(circle one for each item)*	MUCH IMPROVED	A BIT IMPROVED	NOT MUCH CHANGE	A BIT WORSE	MUCH WORSE
Remembering things about family and friends—e.g., occupations, birthdays, addresses	1	2	3	4	5
Remembering things that have happened recently	1	2	3	4	5
Recalling conversations a few days later	1	2	3	4	5
Remembering their own address and telephone number	1	2	3	4	5
Remembering what day and month it is	1	2	3	4	5
Remembering where things are usually kept	1	2	3	4	5
Handling money for shopping	1	2	3	4	5
Handling financial matters—e.g., a pension, dealing with the bank	1	2	3	4	5
Handling everyday arithmetic problems—e.g., knowing how much food to buy, knowing how long between visits from family or friends	1	2	3	4	5
Making decisions on everyday matters	1	2	3	4	5

SCORE:_____ **(Divide by 10. An average of ≥3.3 may indicate cognitive decline and requires further assessment.)**

NOTE: Not complete. To administer the full questionnaire, see the Alzheimer's Association Cognitive Assessment Toolkit at *alz.org/hcps*.
Adapted from Jorm AF. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly. *Psychol Med.* 1994;24:145-153.