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DND Dementia and Neurocognitive Disorder

Review Article

Lecanemab: Appropriate Use Recommendations by Korean Dementia Association

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ABSTRACT

Lecanemab (product name Leqembi®) is an anti-amyloid monoclonal antibody treatment approved for use in Korea for patients with mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease. The Korean Dementia Association has created recommendations for the appropriate use of lecanemab to assist clinicians. These recommendations include selecting patients for administration, necessary pre-administration tests and preparations,

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The authors have no financial conflicts of interest.

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administration methods, monitoring for amyloid related imaging abnormalities (ARIA), and communication with patients and caregivers. Lecanemab is recommended for patients with MCI or mild dementia who confirmed positive amyloid biomarkers, and should not be administered to patients with severe hypersensitivity to lecanemab or those unable to undergo magnetic resonance imaging (MRI) evaluation. To predict the risk of ARIA before administration, apolipoprotein E genotyping is conducted, and regular brain MRI evaluations are recommended to monitor for ARIA during treatment. The most common adverse reactions are infusion-related reactions, which require appropriate management upon occurrence. Additional caution is needed when co-administering with anticoagulants or tissue plasminogen activator due to the risk of macrohemorrhage. Clinicians should consider the efficacy and necessary conditions for administration, as well as the safety of lecanemab, to make a comprehensive decision regarding its use.

Keywords: Lecanemab; Alzheimer's Disease; Amyloid; Magnetic Resonance Imaging; Monoclonal Antibody

INTRODUCTION

The approval of lecanemab (brand name Leqembi®) for Alzheimer's disease (AD), a disease still considered incurable, is bringing significant changes to the paradigm of AD treatment. The United States Food and Drug Administration (U.S. FDA) approved the use of lecanemab for patients with early symptoms of AD in July 2023, based on the results of phase 3 clinical trials.[1] Following this, Japan approved lecanemab in September 2023, and South Korea also approved lecanemab in May 2024 following China's approval in January 2024. Following the approval of the drug, regulatory agencies in each country issued prescribing information regarding the drug's usage, dosage, administration methods, contraindications, precautions, side effects, storage, and handling.[2,3] The Korea Ministry of Food and Drug Safety (MFDS) also provided expert explanatory materials that include the drug's usage, dosage, precautions for use, and other relevant information.[4]

To maximize the therapeutic effects of lecanemab and ensure its safe use in clinical practice, supplementary information beyond prescribing information and expert explanatory materials is essential. This includes details on the necessary hospital facilities for administering lecanemab, criteria for identifying patients who are likely to benefit from the drug with minimized side effects, comprehensive explanations of potential adverse effects, and guidance on monitoring and managing these side effects effectively. To this end, the Alzheimer's Disease and Related Disorders Therapeutics Work Group (ADRD-TWG) in the United States has issued Appropriate Use Recommendations (AUR) for lecanemab, which encompass these considerations.[5]

The Korean Dementia Association (KDA) recommendations for appropriate use of lecanemab aim to provide appropriate recommendations tailored to Korean circumstances to help clinicians use lecanemab safely and effectively. These recommendations will cover patient selection for lecanemab treatment, necessary pre-treatment examinations and preparations, administration methods, monitoring and management of amyloid related imaging abnormalities (ARIA) and infusion-related adverse reactions, as well as consultations with patients and caregivers. The ultimate goal of these recommendations is to minimize side effects, maximize efficacy, and optimize the use of lecanemab.

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METHODS

This AUR was developed by a special committee organized by the KDA to ensure the appropriate use of lecanemab. The special committee consists of 11 experts selected from the board members of the KDA, all of whom have extensive experience in conducting clinical trials of AD drugs and in treating patients with mild cognitive impairment (MCI) and dementia. To draft the AUR, the committee held a total of seven meetings starting in March 2024, and the guidelines were reviewed and approved by the entire board of the KDA in September 2024. This guideline is primarily based on the most up-to date clinical trial data on lecanemab as of the publication date,[1] expert explanatory materials from the Korea MFDS,[4] the U.S. FDA prescription information,[2] optimal use guidelines from Japanese Ministry of Health, Labour and Welfare (MHLW),[3] and the ADRD-TWG recommendations for lecanemab.[5] The Korean version of the AUR is provided as **Supplementary File 1** for clinicians in Korea.

Summary of results from the phase 3 lecanemab clinical trial

Lecanemab is an immunoglobulin G1 anti-amyloid monoclonal antibody that primarily shows a high binding affinity to protofibrillar forms of amyloid plaques. In the phase 3 clinical trial, lecanemab demonstrated both significant reductions in amyloid plaques and clinical efficacy in early AD (MCI or mild dementia due to AD), leading to its approval by the U.S. FDA as the first disease modifying therapy (DMT) for AD. In the phase 2 clinical trial, a significant reduction in amyloid plaque was observed in amyloid positron emission tomography (PET) scans of early AD patients who were treated for 18 months, and the treatment group showed a significant delay in the worsening of cognitive decline compared to the placebo group, as measured by the primary outcome, the Alzheimer's Disease Composite Score (ADCOMS).[6] The phase 3 clinical study of lecanemab was conducted under the title clarity AD.[1] A total of 1,795 patients with a Mini-Mental Status Examination (MMSE) score of 22–30 and positive amyloid PET were randomly assigned in a 1:1 ratio to the treatment or placebo groups, receiving either 10 mg/kg of lecanemab or placebo every two weeks for 18 months. Among the patients participating in the study, 69% were carriers of the apolipoprotein E ε4 allele (*APOE4*), and 31% were non-carriers. The results of the study showed that the treatment group exhibited 0.45 points less worsening in the Clinical Dementia Rating (CDR)-Sum of Boxes, the primary outcome measure, compared to the placebo group after 18 months, indicating a 27% slower decline in cognitive function. Similar statistically significant results were observed in the secondary measures, including the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14), the ADCOMS, and the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for MCI (ADCS-MCI-ADL). Additionally, a statistically significant reduction in amyloid plaques was observed in the treatment group (−59.12 centiloids; 95% confidence interval, −62.64, −55.60; p<0.001). Based on these results, the U.S. FDA formally approved the use of lecanemab in July 2023.

The most commonly observed side effect in the lecanemab treatment group was infusion-related reactions (26.3%), followed by ARIA. For ARIA, ARIA-H (hemosiderin/hemorrhage) was 17.3% of patients, ARIA-E (edema/effusion) in 12.6%, and headache in 11.1%. Particularly, ARIA was more frequently observed in carriers of the *APOE4*. Most patients with ARIA observed on magnetic resonance imaging (MRI) were asymptomatic, with symptomatic ARIA occurring in 3% (29/898) of the entire treatment group, and severe symptoms were observed in 0.7% (6/898).[1,2] In a separate analysis of 141 patients in the

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lecanamab treatment group from the Asian cohort,[7] infusion-related reactions were reported in 12.4% (Japan: 10.2%, Korea: 13%), and ARIA-H was reported in 14.4% of the Asian group (Japan: 14.8%, Korea: 11.1%). ARIA-E was observed in 6.5% of the Asian group (Japan: 4.5%, Korea: 5.6%). Symptomatic ARIA-E and ARIA-H were not reported in the Asia group.

RECOMMENDATIONS

To which patients should lecanemab be administered?

Clinical criteria recommendation for appropriate patient selection in the use of lecanemab

The KDA recommendations are primarily based on the registration criteria and inclusion/exclusion criteria of the phase 3 clinical trial[1] and the ADRD-TWG recommendations.[5] Therefore, the KDA recommendations recommend the use of lecanemab in patients with MCI due to AD and mild AD dementia.[1,5] To confirm amyloid pathology, an amyloid PET scan or cerebrospinal fluid (CSF) test is required. The diagnostic criteria for MCI due to AD and mild AD dementia, as in the phase 3 clinical trial of lecanemab, is based on the National Institute on Aging-Alzheimer's Association (NIA-AA) clinical criteria of MCI due to AD with intermediate likelihood[8] and probable AD dementia with evidence of the AD pathological process.[9] Since the phase 3 clinical trial of lecanemab only included patients with MCI and mild dementia, limited to those with a CDR score of 0.5–1, the efficacy of lecanemab has not been established in patients with normal cognition or moderate to severe AD dementia.

As such, this AUR from KDA recommends the use of lecanemab for patients who meet the diagnostic criteria for MCI due to AD and mild AD dementia, confirmed to be amyloid biomarker—positive (via amyloid PET or CSF testing), as outlined in **Table 1**.

Considerations for patient selection in clinical trial

The recommendations of the lecanemab phase 3 clinical trial, ADRD-TWG, and KDA are summarized in **Table 2**. Looking at the inclusion criteria, it is noteworthy that both Korea MFDA and U.S. FDA prescribing information and AUR allow for broader patient eligibility

Table 1. Diagnostic criteria for MCI due to AD and probable mild AD dementia

Diagnosis classification	Diagnosis criteria
MCI due to AD (MCI due to AD with intermediate likelihood based on NIA-AA diagnostic criteria)[8]	- Cognitive concerns by the patient, knowledgeable informant, or the physician - Objective impairment in one or more cognitive domains including memory, executive function, attention, language, and visuospatial skills - Generally preserved activities of daily living - No dementia - Positive AD biomarker
Dementia (core clinical criteria for all-cause dementia based on NIA-AA diagnostic criteria)[9]	- Cognitive or behavioral impairment involving a minimum of two of the following domains: memory, executive function, visuospatial function, language, behavior - Cognitive impairment detected and diagnosed through a combination of 1) history-taking from the patient and a knowledgeable informant and 2) an objective cognitive assessment - Symptoms interfere with the ability to function at work or perform usual activities - Decline from previous levels of functioning - Symptoms not explained by delirium or major psychiatric disorder
Probable Alzheimer's disease dementia with evidence of the AD pathophysiological process[9]	- Meets criteria for dementia - History of worsening of cognition by report or observation - The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories: • Amnestic presentation • Nonamnestic presentations associated with amyloid positive confirmation - Positive AD biomarker
Cognitive impairment severity	CDR 0.5–1 to define MCI and mild AD dementia

MCI: mild cognitive impairment, AD: Alzheimer's disease, NIA-AA: National Institute on Aging-Alzheimer's Association, CDR: Clinical Dementia Rating.

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Table 2. Lecanemab phase 3 clinical trial, ADRD-TWG and KDA recommendations comparison

Lecanemab phase 3 clinical trial	ADRD-TWG recommendations	KDA recommendations
Inclusion criteria		**Recommended indications for medication use**
Diagnosis of MCI due to AD (global CDR of 0.5) and mild AD dementia (global CDR score of 0.5 to 1.0) (Table 1)	Clinical diagnosis of MCI due to AD and mild AD dementia (Table 1) MMSE score of 22–30	Clinical diagnosis of MCI due to AD and mild AD dementia (Table 1) CDR 0.5–1 to define MCI and mild AD dementia
CDR memory score 0.5 or higher Wechsler memory scale IV-logical memory II test showing objective memory impairment below 1 standard deviation compared to age-adjusted mean score	Clinical diagnosis of MCI due to AD and mild AD dementia (Table 1) MMSE score of 22–30	Clinical diagnosis of MCI due to AD and mild AD dementia (Table 1) CDR 0.5–1 to define MCI and mild AD dementia
Positive biomarker for brain amyloid pathology	Positive amyloid PET or CSF studies indicative of AD	Positive amyloid PET or CSF studies indicative of AD
Age 50–90	Physician judgement used for patients outside the 50–90 year age range	Physician judgement used for patients outside the 50–90 year age range
MMSE score >22 at screening and Baseline and <30 at screening and baseline	MMSE 22–30 or other cognitive screening instrument with a score compatible with early AD	MMSE score of 22–30 or a corresponding score on tests indicating early AD However, in cases where the MMSE score is below 22, physicians may make a judgment based on the average score and standard deviation according to age and education level in the Korean standard population
BMI greater than [>]17 and less than [<] 35 at screening	Physician judgement used for patients at the extremes of BMI	Physician judgement used for patients at the extremes of BMI (less than 17 and greater than 35)
If receiving an acetylcholinesterase inhibitor (donepezil, rivastigmine, galantamine) or memantine or both must be on a stable dose for at least 12 weeks prior to baseline	Patients may be on cognitive enhancing agents (donepezil, rivastigmine, galantamine, or memantine) for AD; patients may not be on aducanumab	Other Alzheimer's disease treatments approved in Korea (donepezil, rivastigmine, galantamine, memantine) can be used concurrently.
Unless otherwise stated, participants must have been on stable doses of all other (that is, non-AD-related) permitted concomitant medications for at least 4 weeks prior to baseline	Patients may be on standard of care for other medical illnesses (see below for specifics regarding anticoagulation)	Patients may be on standard of care for other medical illnesses (see below for precautions regarding anticoagulation)
Have an identified study partner	Have a care partner or family member(s) who can ensure that the patient has the support needed to be treated with lecanemab	It is recommended that a caregiver be available to provide support during the lecanemab treatment period
Provide written informed consent	Patients, care partners, and appropriate family members should understand the requirements for lecanemab therapy and the potential benefit and potential harm of treatment	Patients and caregivers should have a clear understanding of the requirements for lecanemab treatment, as well as the associated benefits and risks
Exclusion criteria		**Cautionary considerations**
Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the participant's AD	Any medical, neurologic, or psychiatric condition that may be contributing to the cognitive impairment or any non-AD MCI or dementia	In cases where significant cognitive impairment is caused by medical, neurological, or psychiatric conditions other than AD
Contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (e.g., in skull and cardiac devices other than those approvedas safe for use in MRI scanners).	Patients unable to undergo MRI due to claustrophobia, pacemaker, defibrillator, or metal implants	Patients unable to undergo MRI**
If any of the following findings are present on the screening brain MRI: · More than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter) · A single macrohemorrhage >10 mm at greatest diameter · An area of superficial siderosis · Evidence of vasogenic edema · Multiple lacunar infarcts or stroke involving a major vascular territory · Severe small vessel; or other major intracranial pathology	In the case where any of the following findings are present on brain MRI: · More than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter) · A single macrohemorrhage >10 mm at greatest diameter; · An area of superficial siderosis · Evidence of vasogenic edema · More than 2 lacunar infarcts or stroke involving a major vascular territory · Severe subcortical hyperintensities consistent with a Fazekas score of 3 · Evidence of ABRA or CAA-ri · Other major intracranial pathology that may cause cognitive impairment	In the case where any of the following findings are present on brain MRI: · More than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter) · A single macrohemorrhage >10 mm at greatest diameter · An area of superficial siderosis · Evidence of vasogenic edema · More than 2 lacunar infarcts or stroke involving a major vascular territory · Severe subcortical hyperintensities consistent with a Fazekas score of 3 · Evidence of ABRA or CAA-ri · Other major intracranial pathology that may cause cognitive impairment

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Table 2. (Continued) Lecanemab phase 3 clinical trial, ADRD-TWG and KDA recommendations comparison

Lecanemab phase 3 clinical trial	ADRD-TWG recommendations	KDA recommendations
Evidence of other clinically significant lesions on brain MRI at screening that could indicate a dementia diagnosis other than AD	MRI evidence of a non-AD dementia	MRI evidence of a non-AD dementia
History of TIA, stroke, or seizures within 12 months of screening	Recent history (within 12 months) of stroke or TIA or any history of seizures	Recent history (within 12 months) of stroke or TIA or any history of seizures
Any psychiatric diagnosis or symptoms (example, hallucinations, major depression, or delusions) that could interfere with study procedures in the participant	Mental illness (e.g, psychosis) that interferes with comprehension of the requirements, potential benefit, and potential harms of treatment and are considered by the physician to render the patient unable to comply with management requirements	Mental illness (e.g, psychosis) that interferes with comprehension of the requirements, potential benefit, and potential harms of treatment and are considered by the physician to render the patient unable to comply with management requirements
Geriatric Depression Scale score >8 at screening	Major depression that will interfere with comprehension of the requirements, potential benefit, and potential harms of treatment; patients for whom disclosure of a positive biomarker may trigger suicidal ideation. Patients with less severe depression or whose depression resolves may be treatment candidates	Major depression that will interfere with comprehension of the requirements, potential benefit, and potential harms of treatment; patients for whom disclosure of a positive biomarker may trigger suicidal ideation. Patients with less severe depression or whose depression resolves may be treatment candidates
In cases where there is hypersensitivity to lecanemab or other monoclonal antibody treatments	Not applicable	Lecanemab administration is contraindicated in cases of severe hypersensitivity to lecanemab**
Any immunological disease which is not adequately controlled, or which requires treatment with immunoglobulins, systemic monoclonal antibodies (or derivatives of monoclonal antibodies), systemic immunosuppressants, or plasmapheresis during the study	Any history of immunologic disease (e.g., lupus erythematosus, rheumatoid arthritis, Crohn's disease) or systemic treatment with immunosuppressants, immunoglobulins, or monoclonal antibodies or their derivatives	In cases of immune diseases (e.g., lupus erythematosus, rheumatoid arthritis, Crohn's disease) or when receiving systemic immunosuppressants, immunoglobulins, or monoclonal antibody treatments
Participants with a bleeding disorder that is not under adequate control (including a platelet count <50,000 or INR >1.5 for participants who are not on anticoagulant treatment, example, warfarin	Patients with a bleeding disorder that is not under adequate control (including a platelet count <50,000 or INR >1.5 for participants who are not on anticoagulant)	Patients with a bleeding disorder that is not under adequate control (including a platelet count <50,000 or INR >1.5 for participants who are not on anticoagulant)
Participants who are on anticoagulant therapy should have their anticoagulant status optimized and be on a stable dose for 4 weeks before screening	Patients on anticoagulants (coumadin, dabigatran, edoxaban, rivaroxaban, apixaban, betrixaban, or heparin) should not receive lecanemab; tPA should not be administered to individuals on lecanemab	Patients taking anticoagulants (such as warfarin, heparin, dabigatran, edoxaban, rivaroxaban, apixaban, and other new oral anticoagulants). For patients currently receiving lecanemab, the administration of tPA, heparin, or anticoagulants should be determined by weighing the benefits and risks associated with their use
Any other medical conditions (example, cardiac, respiratory, gastrointestinal, renal disease) which are not stably and adequately controlled, or which could affect the participant's safety or interfere with the study assessments	Unstable medical conditions that may affect or be affected by lecanemab therapy	Unstable medical conditions that may affect or be affected by lecanemab therapy

ADRD TWG: Alzheimer's Disease and Related Disorders Therapeutics Work Group, KDA: Korean Dementia Association, MMSE: Mini-Mental Status Examination, MCI: mild cognitive impairment, AD: Alzheimer's disease, CDR: Clinical Dementia Rating, PET: positron emission tomography, CSF: cerebrospinal fluid, BMI: body mass index, MRI: magnetic resonance imaging, ABRA: amyloid beta-related angiitis, CAA-ri: cerebral amyloid angiopathy-related inflammation, TIA: transient ischemic attacks, INR: international normalized ratio, tPA: tissue plasminogen activator.
**In alignment with the contraindications presented by Korea Ministry of Food and Drug Safety, the KDA also recommends these two cases as contraindications for lecanemab use.

compared to the clinical trial' inclusion criteria. For example, the expert explanatory materials from Korea MFDS[4] and prescribing information from the U.S. FDA[2] only state that lecanamab is indicated for the treatment of MCI due to AD or mild AD dementia, without specifying detailed inclusion criteria. Similarly, the AUR from the ADRD-TWG[5] indicates that, in terms of age and body mass index, the drug may be used at the clinician's discretion, even if these parameters fall outside the criteria used in the phase 3 clinical trial. Furthermore, the AUR from the ADRD-TWG[5] does not specify any requirements regarding the stabilization period for concomitant medications previously used by the patient. While the phase 3 clinical trial of lecanemab included memory impairment as part of the inclusion criteria, the AUR from ADRD-TWG[5] and the guidelines from Japanese MHLW[3] do not

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specifically mention this, thus allowing for the possibility of using lecanemab in patients who show cognitive decline beyond just memory impairment.

The inclusion criteria of the KDA recommendations were based on those from the phase 3 clinical trial of lecanemab and the ADRD-TWG recommendations. However, applying the 22–30 point range for the MMSE, as suggested by the phase 3 trial of lecanemab and the guidelines from the Japanese MHLW, may exclude elderly individuals with low education levels in Korea from being eligible for treatment, even if they are in the early stage of MCI. For example, in the Korean standard population, the average MMSE score for illiterate individuals aged 70 and older is below 22. Therefore, for patients with MMSE scores less than 22, it is recommended that clinicians decide whether to use lecanemab based on the patient's age and education level in the Korean standard population, considering the average scores and standard deviations.

In terms of exclusion criteria, the prescription information of Korea MFDS[4] and U.S. FDA[2] list only severe hypersensitivity to lecanemab as a contraindication. The guidelines from Japanese MHLW[3] in addition to hypersensitivity, list pre-treatment brain MRI findings such as brain edema, ≥5 microhemorrhages, superficial siderosis, and >1 cm macrohemorrhages as contraindications. In contrast, the ADRD-TWG recommendations set stricter exclusion criteria in some areas compared to those from the phase 3 clinical trial of lecanemab. For example, in the phase 3 trial, cases where cognitive impairment could have been influenced by non-AD causes were not excluded unless they were severe, but the ADRD-TWG recommendations advise excluding such cases. Additionally, while seizures within 12 months were an exclusion criterion in the phase 3 clinical trial, the ADRD-TWG recommendations suggest excluding patients with a history of seizures at any time, due to the potential association with existing ARIA, until more evidence is gathered. Regarding MRI criteria, the ADRD-TWG sets stricter criteria, including amyloid-beta related angiitis (ABRA) and cerebral amyloid angiopathy-related inflammation (CAA-ri), both of which increase the risk of ARIA. Some items have been added based on new findings from the lecanemab clinical trial. The risk of cerebral hemorrhage increased when lecanemab was co-administered with anticoagulants. Additionally, there was a reported case of a lecanemab-treated patient who developed newly acute cerebral infarction, died after receiving tissue plasminogen activator (tPA), because of cerebral hemorrhages.[10] Based on this, both the Korea MFDS and U.S. FDA prescription information recommend careful consideration and caution when co-administering anticoagulants or tPA with lecanemab. However, the ADRD-TWG recommendations take a stronger stance, prohibiting the concomitant use of these medications with lecanemab, as they do with other exclusion criteria.

The KDA recommendations, referring to the prescribing information from the Korea MFDS and the U.S. FDA, have replaced the term 'exclusion criteria' used in clinical trial with the term 'cautionary considerations' (**Table 2**). However, two conditions that are universally prohibited by both domestic and international prescribing information are 1) severe hypersensitivity to lecanemab and 2) the inability to undergo MRI scans, both of which are also contraindicated by KDA recommendations. For all other conditions, clinicians are recommended to carefully weigh the benefits and risks of treatment based on existing and newly emerging evidence.

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Laboratory tests necessary for the appropriate use of lecanemab

Neuroimaging evaluations

Lecanemab can only be used in patients who have confirmed amyloid pathology through amyloid PET or CSF testing indicative AD. Currently, the amyloid PET ligands available in Korea include florbetaben, flutemetamol, florbetapir, and florapronol. Tau PET, on the other hand, is only available for research purposes in Korea and is not included in the eligibility criteria for clinical studies. Therefore, tau PET is not required when considering lecanemab treatment.

To assess the safety of lecanemab administration, an MRI taken within 12 months before starting the treatment is required. The MRI does not need to use contrast agents but should be at least 1.5T, preferably 3T, and must include T2-weighted/fluid attenuated inversion recovery (FLAIR), T2*-gradient-recalled echo (GRE) or susceptibility-weighted imaging (SWI), and diffusion-weighted imaging (DWI).

As outlined in **Table 2**, if any of the following findings are present on the brain MRI, there is a higher risk of adverse events, and caution is required. The ADRD-TWG recommends against administering lecanemab if the MRI shows a single macrohemorrhage >10 mm in diameter, more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), or the presence of superficial siderosis. Additionally, it is recommended to avoid lecanemab treatment if the MRI shows CAA-ri (**Table 3**), ABRA,[11,12] vasogenic edema, severe subcortical hyperintensities, more than 2 lacunar infarcts, stroke involving a major vascular territory, or other major intracranial pathology that may cause cognitive impairment. However, since the Korea MFDS and U.S. FDA does not specifically mention these conditions, this KDA recommendations include them under 'cautionary considerations'.

According to the ADRD-TWG recommendations and the results of the phase 3 clinical trial, caution is required when administering lecanemab in cases of cerebral contusion, encephalomalacia, cerebral aneurysm and vascular malformations, central nervous system infections, or brain tumors (other than meningiomas and arachnoid cysts). Since the assessment of ARIA from lecanemab treatment cannot be substituted by computed tomography (CT) scans instead of MRI, if a patient has claustrophobia or is otherwise unable to undergo an MRI, lecanemab cannot be used.

APOE genotyping

APOE4 carriers have an increased risk of developing AD and CAA-ri/ABRA, and this risk is higher in *APOE4* homozygotes compared to *APOE4* heterozygotes.[13] The risk of ARIA due to lecanemab is also related to *APOE4*, with *APOE4* carriers having an increased risk of ARIA. In particular, the risk of symptomatic ARIA and recurrent ARIA is elevated. This tendency is significantly higher in *APOE4* homozygotes compared to *APOE4* heterozygotes. Therefore, it is recommended to consider *APOE* genotyping in patients for whom lecanemab treatment is

Table 3. MRI criteria for probable cerebral amyloid angiopathy-related inflammation[11]

MRI criteria for probable cerebral amyloid angiopathy-related inflammation
• Age ≥40 years of age
• Presence of ≥1 of the following clinical features: headache, decrease in consciousness, behavioral change, or focal neurological signs and seizures; the presentation is not directly attributable to an acute ICH
• MRI shows unifocal or multifocal WMH lesions (corticosubcortical or deep) that are asymmetric and extend to the immediately subcortical white matter; the asymmetry is not due to past ICH
• Presence of ≥1 of the following cortico-subcortical hemorrhagic lesions: cerebral macrobleed, cerebral microbleed, or cortical superficial siderosis
• Absence of neoplastic, infectious, or other cause

MCI: mild cognitive impairment, ICH: intracerebral hemorrhage, WMH: white matter hyperintensity.

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planned, and based on the *APOE* genotype results, the potential risk of the treatment should be discussed with the patients and their caregivers.

Cerebrospinal fluid test and blood test

The diagnosis of AD using CSF testing is widely recognized globally, and an officially approved testing method is also available in Korea. In fact, in the phase 3 clinical trial of lecanemab, patients were enrolled not only based on amyloid PET results but also on CSF test results showing increased phosphorylated tau and decreased amyloid-beta (Aβ) 42, leading to a diagnosis of AD.[1] Therefore, patients diagnosed with AD using CSF testing may still be eligible for lecanemab use, even if amyloid PET results are unavailable.

On the other hand, making a definitive diagnosis of AD using blood tests is still premature. While many studies have provided evidence that elevated plasma phosphorylated tau, a decreased Aβ 42/40 ratio, and abnormal profiles from various biomarker combinations may be useful for diagnosing and monitoring AD, no blood-based biomarker has yet been approved as sufficient for selecting appropriate candidates for lecanemab treatment. Therefore, it is currently not possible to make a definitive diagnosis of AD or determine eligibility for lecanemab based on blood biomarkers.[14]

Considerations for lecanemab administration in real-world clinical setting

Proper storage, dosage, and administration of lecanemab

Lecanemab is supplied in vials containing either 500 mg/5 mL (100 mg/mL) or 200 mg/2 mL (100 mg/mL) and should be stored refrigerated at 2°C–8°C (35°F–47°F). It should be kept in its original box to protect it from light and should not be frozen or shaken.[4] The recommended dosage of lecanemab is 10 mg/kg, administered intravenously over approximately 1 hour once every two weeks. If a dose is missed, the patient should visit the clinic as soon as possible to receive the injection, and the next injection should be administered two weeks later.

Lecanemab should not be administered via intravenous push or bolus injection. The drug must be diluted prior to intravenous infusion, and the following specific instructions should be followed for dilution: Before administration, visually inspect the solution for particulate matter and discoloration, ensuring that the solution is milky and colorless to pale yellow. If visible particles are observed, the vial should be discarded. The dose should be calculated based on the patient's actual body weight, and the required number of vials should be determined accordingly. Each vial contains lecanemab at a concentration of 100 mg/mL. The appropriate volume should be withdrawn from the vial for a single dose and added to a 250 mL bag of 0.9% sodium chloride injection solution. Each vial is single-use, and any unused portion should be discarded. The infusion bag containing the diluted solution should be gently inverted to ensure thorough mixing, but it should not be shaken. Before administering to the patient, the diluted solution should be allowed to reach room temperature, and the entire diluted solution should be infused intravenously over approximately 1 hour using an intravenous line with a terminal low-protein binding 0.2-micron in-line filter. After the infusion, the infusion line should be flushed with 0.9% sodium chloride solution to ensure the full dose is administered. Typically, after the infusion is completed, 100 mL of 0.9% sodium chloride solution is connected and is flushed with 10–25 cc. According to the Korean MFDS's guidelines, the diluted solution has been proven to be chemically and physically stable for up to 24 hours at room temperature (25°C), but emphasizes immediate use from a microbiological perspective. Unless diluted under controlled and validated aseptic conditions, it is generally recommended not to exceed 24 hours at 2°C–8°C. The U.S. FDA prescribing

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Table 4. Resources required by physicians or medical institutions for the use of lecanemab

Resources required by physicians or medical institutions for the use of lecanemab
· Ensure the availability of dementia specialists proficient in diagnosing MCI due to AD or mild AD dementia.
· Be capable of performing and interpreting *APOE* genotyping.
· Have radiologists, neurologists, or other specialists available for identifying and evaluating cerebrovascular lesions and ARIA.
· Have specialized medical personnel skilled in conducting and interpreting amyloid PET or cerebrospinal fluid tests.
· Ensure the presence of neurologists or relevant experts with experience in managing seizures and status epilepticus that may arise from ARIA symptoms.
· Equip facilities for bi-weekly intravenous administration of lecanemab and personnel to monitor for adverse drug reactions.

MCI: mild cognitive impairment, AD: Alzheimer's disease, *APOE*: apolipoprotein E, ARIA: amyloid related imaging abnormalities, PET: positron emission tomography.

information advises not to store the diluted solution for more than 4 hours at refrigerated (2°C–8°C) or room temperature (up to 30°C). Therefore, it is recommended to use the diluted solution as soon as possible and not freeze it, even if the storage time is extended.

Resources required for safe administration of lecanemab treatment

Table 4 outlines the resources necessary for the safe administration of lecanemab treatment.[5] Clinicians should be able to assess the cognitive and mental status of all patients with MCI or mild dementia to determine whether they are suitable candidates for treatment. A recent (usually within one year) MRI should be evaluated to rule out non-AD causes of cognitive impairment, identify any cerebrovascular factors requiring attention, and confirm AD pathology through brain amyloid PET imaging or CSF testing for amyloid and tau.

Since lecanemab is administered intravenously every two weeks, there needs to be an outpatient infusion facility or injection room available. Necessary resources include one 250 mL bag of saline for dilution, one 100 mL bag of saline for flushing, infusion lines, intravenous catheters, filters, infusion pumps, and a refrigerator capable of storing lecanemab at 2°C–8°C.

Preparation for adverse event monitoring is also essential. Regular MRI scans should be conducted according to the recommended schedule, and if patients exhibit symptoms related to ARIA, an emergency MRI should be performed. Clinicians should have the clinical knowledge and skills to assess suspected ARIA symptoms and be prepared to respond with urgent MRI scans and appropriate management.

Additionally, the ADRD-TWG recommendations emphasize the need for medical personnel who can recognize and appropriately manage infusion-related reactions.[5] If a patient is deemed eligible for lecanemab treatment but the necessary resources are unavailable, it is recommended to refer the patient to a medical facility that possesses the required resources.

Monitoring and management of possible adverse reactions during lecanemab treatment

Monitoring and treatment of infusion-related reactions

According to prescription information from the Korea MFDS, caution is advised in the event of infusion-related reactions, and these should be carefully monitored and treated. In the phase 3 clinical trial of lecanemab, infusion-related reactions occurred in 26.4% of patients in the lecanemab group and 7.4% of patients in the placebo group. Common symptoms included fever, chills, headache, rash, nausea, vomiting, abdominal discomfort, and elevated blood pressure. Most of these reactions occurred during the first two treatments,[6] with 75% occurring during the first infusion. The majority (96%) of infusion-related reactions were mild to moderate in severity (grade 1 or 2, as outlined in **Table 5**),[15] and generally resolved

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Table 5. Infusion-related reaction grade classification[15]

CTCAE v5.0 term	Infusion-related adverse reaction
Grade 1	Mild transient reaction; infusion interruption not indicated; intervention not indicated
Grade 2	Infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, acetaminophen, NSAIDs, narcotics, i.v. fluids); prophylactic medication indicated for ≤24 hours
Grade 3	Prolonged recurrence of symptoms following initial improvement; hospitalization may be indicated for clinical sequelae (e.g., poorly controlled hypertension)
Grade 4	Life-threatening consequences; urgent intervention indicated (may require pressor or ventilatory support)
Grade 5	Death

CTCAE: Common Terminology Criteria for Adverse Events (U.S. Department of Health and Human Services), NSAID: nonsteroidal anti-inflammatory drugs.

within 24 hours without requiring hospitalization, allowing management at home. Among these patients, 56% did not take preventive medications for infusion-related reactions during subsequent treatments. Additionally, 63% of those who took prophylactic medication did not experience further infusion-related reactions afterward.[1]

The ADRD-TWG recommendations suggest discontinuing the infusion if a Grade 2 infusion reaction occurs.[5] For milder cases, the patient can be treated with diphenhydramine and acetaminophen. In cases of more severe symptoms, oral dexamethasone (0.75 mg per day for 2–3 days) or oral methylprednisolone (80 mg twice daily for 2–3 days) is recommended. The diphenhydramine or acetaminophen may be administered every 4–6 hours until symptoms have fully resolved. Following an infusion reaction, it is recommended that patients receive premedications with oral diphenhydramine 25–50 mg and oral acetaminophen 650–1,000 mg 30 minutes prior to the next infusion. Low dose oral dexamethasone (0.75 mg 6 hours before infusion) or oral methylprednisolone (80 mg 6 hours prior to infusion) can be used for prophylaxis or treatment if diphenhydramine and acetaminophen are ineffective. This prophylactic regimen is recommended to continue until the patient remains asymptomatic both in the clinic and at home after 2–4 additional infusions. If new infusion-related reactions occur, it is recommended to administer oral diphenhydramine 25–50 mg and oral acetaminophen 650–1,000 mg every 4–6 hours, monitoring symptom progression to determine whether additional treatment is necessary. Lastly, for patients who experience a grade 3 or higher infusion-related reaction, it is recommended to discontinue further lecanemab infusions.

However, among the medications suggested by the ADRD-TWG recommendations, there are some that are difficult to prescribe in Korea, and in some cases, the recommended doses are higher than usual doses in Korea. Therefore, this AUR from the KDA recommends the following based on existing literature[16,17] and the opinions of experts who use similar medications in Korea.

If a grade 2 or higher infusion related reaction occurs, the infusion should be stopped. For mild symptoms, treatment with antihistamines (e.g., intravenous chlorpheniramine 4 mg) and acetaminophen is recommended. In the case of severe symptoms, steroids should be added to the treatment. Steroids such as intravenous methylprednisolone (100 mg or 0.5–1 mg/kg) or prednisolone (1 mg/kg) may be considered, and adjustments to other steroid medications can be made based on the patient's condition and the clinician's judgment. For mild-to-moderate skin hypersensitivity reactions, antihistamines or topical corticosteroid creams can be considered. If the patient has returned home, it is recommended to call the patient or caregiver on the same day to assess whether the symptoms have improved.

Patients who have experienced a grade 2 or higher infusion-related reaction can be considered for premedication before the next infusion. Intravenous antihistamines and oral

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acetaminophen should be administered 30–60 minutes before the infusion, and steroids can be used as a preventive treatment based on the clinician's judgment. Intravenous methylprednisolone can also be considered as a steroid option, but other antihistamines, corticosteroids, or anti-inflammatory agents can be substituted based on each institution's guidelines. This prophylactic regimen should continue before lecanemab administration until there are no further adverse reactions after 2–4 additional infusions. For patients who experience a grade 3 or higher infusion-related reaction, it is recommended to stop the infusion immediately and permanently discontinue further lecanemab administration.

In the case of grade 4, severe adverse reactions, each institution should have pre-established management plans based on the institution's characteristics and availability of support staff, and should prepare multidisciplinary discussions and criteria for intensive care unit (ICU) admission. If adverse reactions such as wheezing, severe difficulty breathing, cyanosis, hoarseness, difficulty speaking, severe swelling of the tongue or uvula making it hard to swallow, hypotension, or shock occur, administer intramuscular epinephrine (mid-outer thigh), intravenous antihistamines, intravenous methylprednisolone, and consider O_2 administration. In the case of hypotension or shock, saline should be administered at the maximum infusion rate. Reassess symptoms and perform a basic physical examination 5 minutes after the epinephrine injection. If symptoms persist or worsen, administer an additional intramuscular dose of epinephrine (up to a total of 3 doses, at least 5 minutes between each dose). This information is provided as a reference, and it is recommended to adapt it based on the specific practices of the institution.

When administering lecanemab for the first time, it is recommended to observe the patient in the hospital for at least 3 hours to monitor for infusion-related adverse reactions. For the second and third infusions, a 2-hour observation period is recommended, and if no infusion-related adverse reactions occur, a 30-minute observation period is recommended for subsequent infusions.

Understanding ARIA

1) Definition of ARIA

ARIA refers to abnormal findings on MRI that can appear in AD patients receiving anti-amyloid immunotherapy.[18] ARIA is classified into ARIA-E and ARIA-H,[19,20] and both can occur simultaneously. ARIA-E refers to vasogenic edema in the brain parenchyma or sulcal effusion visible on MRI (**Fig. 1**). Vasogenic edema appears as an increased MR signal on T2-weighted/FLAIR imaging and is generally transient, without association with tissue necrosis or cytotoxic edema. ARIA-H refers to hemosiderin deposition, indicating microhemorrhages (≤10 mm) in brain tissue and/or superficial siderosis in the subarachnoid space. ARIA-H is detected using iron-sensitive imaging techniques such as T2*-GRE and SWI.[21]

2) Pathophysiology of ARIA

ARIA is primarily diagnosed based on imaging, and the exact mechanism of occurrence is not yet clearly understood. However, several hypotheses can be considered.

(1) Cerebral amyloid angiopathy (CAA) and CAA-ri

In AD, Aβ deposits also occur in cerebral blood vessels, and the ability to clear Aβ via the perivascular pathways is reduced. CAA is a vascular disorder characterized by Aβ deposition in the walls of cerebral blood vessels (**Fig. 2**).[22] CAA shares many clinical, pathophysiological, and neuroimaging characteristics with ARIA.[18,22-24] One of the most important pieces of evidence linking the pathophysiology of ARIA and CAA is the occurrence of CAA-ri in the

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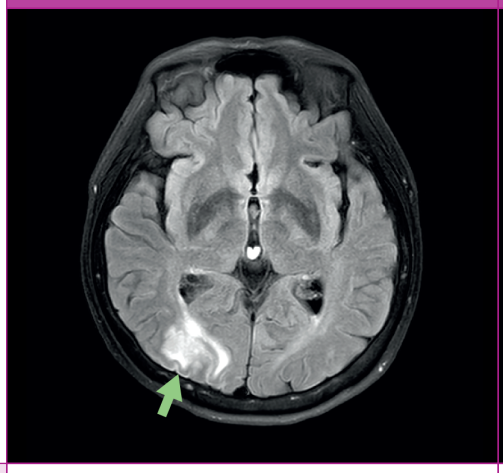
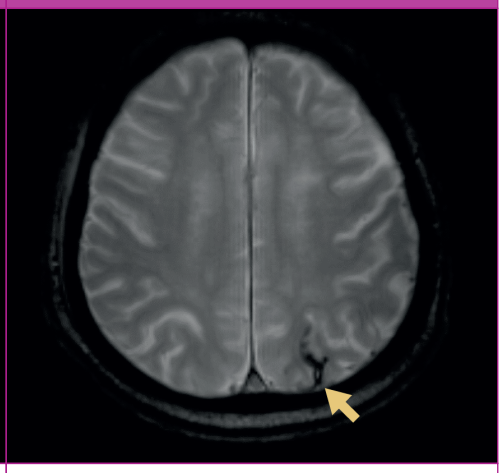
		ARIA-E	ARIA-H
			
Major diagnostic imaging sequence		FLAIR	T2* GRE (or SWI)
Main findings on MRI		FLAIR hyperintense DWI negative No contrast enhancement	GRE/SWI hypointense
Characteristics of leakage products		Proteinaceous fluid	Blood degradation products
Site of increased vascular permeability	Parenchyma	Vasogenic edema (parenchymal hyperintensities and gyral swelling)	Microhemorrhage (hemosiderin deposits ≤10 mm) or macrohemorrhages (>10 mm)
	Leptomeninges	Sulcal effusion/exudate (sulcal hyperintensities)	Superficial hemosiderin deposits

Fig. 1. ARIA characteristics.
ARIA-E: amyloid related imaging abnormalities edema/effusion, ARIA-H: amyloid related imaging abnormalities hemosiderin/hemorrhage, FLAIR: fluid attenuated inversion recovery, GRE: gradient-recalled echo, SWI: susceptibility-weighted imaging, MRI: magnetic resonance imaging, DWI: diffusion-weighted imaging, ARIA: amyloid related imaging abnormalities.

early stages of both sporadic and familial AD. CAA-ri involves an autoimmune response to Aβ, triggered by the activation of multinucleated giant cells, microglia containing Aβ, and T cells surrounding Aβ-laden blood vessel walls. Several studies have reported that ARIA shares similarities with CAA-ri in clinical presentation, imaging findings, pathology, and therapeutic response.[23] ARIA-E is thought to be an iatrogenic sign of CAA-ri occurring in AD patients undergoing anti-amyloid immunotherapy. The MRI findings of CAA and CAA-ri closely resemble those of ARIA-H and ARIA-E, respectively.

(2) Anti-amyloid therapy drug administration

ARIA is known to occur as a result of the breakdown of Aβ by anti-amyloid immunotherapy.[19] When anti-amyloid immunotherapy is initiated, monoclonal antibodies bind to Aβ accumulated in the brain tissue and blood vessels. The monoclonal antibodies bound to Aβ, along with large amounts of Aβ, move through the perivascular clearance pathway. As large amounts of Aβ enter the blood vessels, it triggers inflammation in the surrounding arteries, weakening the cohesion of the vessel walls. This increases the permeability of the vessel walls, leading to edema and microhemorrhages (**Fig. 3**).[22] The leakage of proteinaceous fluid and heme-related substances is observed on MRI, which corresponds to ARIA-E (proteinaceous fluid) and ARIA-H (heme-related substances).

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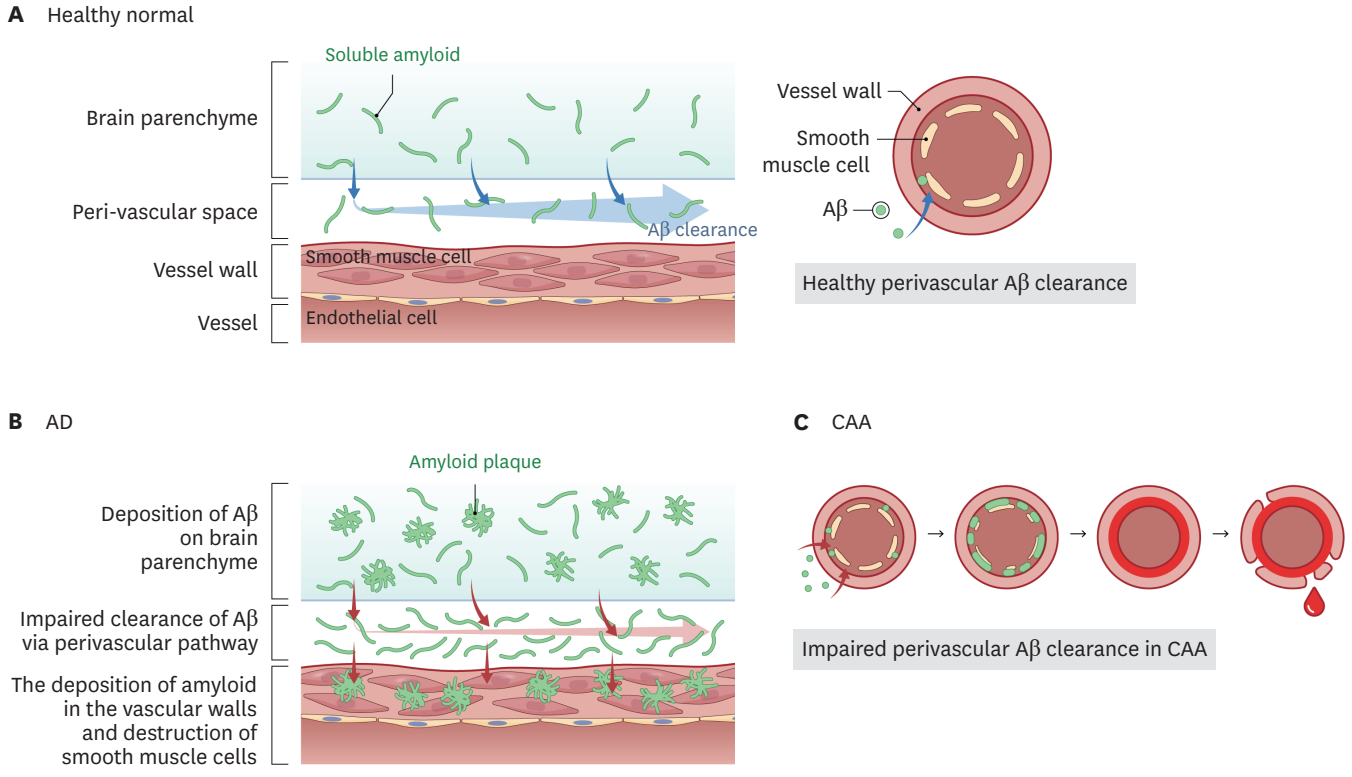

Fig. 2. Impairment of perivascular clearance function in CAA and AD. (A) Healthy normal: in a healthy state, Aβ is removed from the brain along the perivascular space, following the arterial walls, through normal vascular structure and function. (B) AD: in AD, Aβ accumulates in both the brain parenchyma and blood vessels, damaging the vasculature and reducing the clearance of Aβ via the perivascular space. (C) CAA: as the clearance of Aβ via the perivascular space decreases, Aβ accumulates, resulting in a loss of vascular smooth muscle cells and reduced vascular activity, which further decreases Aβ clearance. This continuous decline in Aβ clearance leads to CAA-related vascular lesions, such as hemorrhages and tissue damage, worsening AD pathology.
Aβ: amyloid-beta, AD: Alzheimer's disease, CAA: cerebral amyloid angiopathy.

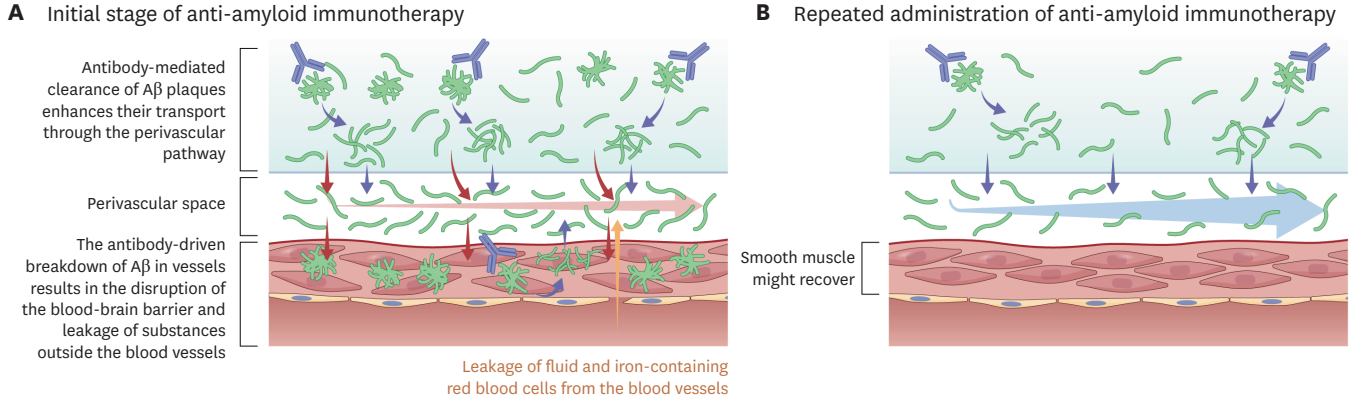

Fig. 3. Hypothesis of ARIA related to amyloid clearance. (A) Initial stage of anti-amyloid immunotherapy: anti-amyloid immunotherapy induces an immune response against Aβ as it moves from the brain parenchyma to the perivascular clearance pathway. This immune response can worsen cerebral amyloid angiopathy, causing leakage of proteinaceous fluid and blood components out of the vessels, leading to amyloid-related imaging abnormalities (ARIA; specifically ARIA-E and ARIA-H). (B) Repeated administration of anti-amyloid immunotherapy: with repeated anti-amyloid immunotherapy, Aβ is continuously cleared via the perivascular clearance pathway, improving the efficiency of this clearance over time. Consequently, the risk of ARIA decreases.
Aβ: amyloid-beta, ARIA: amyloid related imaging abnormalities, ARIA-E: amyloid related imaging abnormalities edema/effusion, ARIA-H: amyloid related imaging abnormalities hemosiderin/hemorrhage.

3) Incidence rate of ARIA

In the phase 3 clinical trial of Lecanemab, the overall incidence rates of ARIA-E, ARIA-H,

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and all types of ARIA (including *APOE4* carriers and non-carriers) were reported to be 12.6%, 17.3%, and 21.5%, respectively.[1,5]

4) Risk factors for ARIA

Key risk factors for ARIA reported in clinical trials of anti-amyloid immunotherapies include drug dosage, the presence of *APOE4*, and pre-treatment MRI findings of microhemorrhages.[18,20,25] In relation to drug dosage, ARIA occurs more frequently with higher doses of the drug and during the early stages of treatment. Higher drug doses and early treatment increase perivascular clearance of Aβ, which in turn elevates vascular permeability, leading to the leakage of proteinaceous fluid and red blood cells, resulting in ARIA-E and ARIA-H, respectively.

Besides drug dosage, the presence of *APOE4* is the most significant risk factor for ARIA. In the phase 3 clinical trial of lecanemab, ARIA-E was observed in 32.6% of *APOE4* homozygotes, 10.9% of *APOE4* heterozygotes, and 5.4% of non-carriers. For ARIA-H, the incidence was 39% in *APOE4* homozygotes, 14.0% in APOE4 heterozygotes, and 11.9% in non-carriers.[1,5] Genetic testing for *APOE* status before initiating therapy may help determine the frequency of safety monitoring in the management.

Patients with cerebral microhemorrhages and superficial siderosis indicative of CAA, especially those who are *APOE4* carriers, have a significantly higher risk of ARIA. In the phase 3 clinical trial of lecanemab, patients with more than 4 microhemorrhages were excluded from the study due to the increased risk of ARIA-E and ARIA-H. [5]

5) Clinical symptoms of ARIA

Most cases of ARIA are asymptomatic. Even in patients with symptomatic ARIA, the symptoms are generally mild, transient, and reversible. Symptoms were reported in 22.1% of patients with ARIA-E and 0.4% of patients with ARIA-H.[1,5] The most commonly reported symptoms, as shown in **Table 6**, include headache, confusion, vomiting, and visual or gait disturbances. However, severe symptoms such as cerebral edema, seizures, and death can occur, which may require hospitalization and treatment (e.g., ICU admission, electroencephalography, steroid therapy, anticonvulsant administration).

6) MRI protocol for ARIA diagnosis

The Alzheimer's Association Research Roundtable Workgroup proposed a minimum standard MRI protocol that can be implemented in various treatment settings, particularly

Table 6. Symptoms observed in symptomatic ARIA patients

Symptoms observed in symptomatic ARIA patients
· Headache
· Confusion
· Visual changes
· Dizziness
· Nausea
· Gait impairment
· Severe ARIA
✓ Seizure
✓ Status epilepticus
✓ Encephalopathy
✓ Stupor
✓ Focal neurological symptoms

ARIA: amyloid related imaging abnormalities.

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Table 7. MRI protocol for the diagnosis of ARIA[26]

Imaging technique	Purpose
T2-FLAIR	ARIA-E (vasogenic edema in brain parenchyma, subarachnoid effusion and exudate)
T2*-GRE (or SWI)	ARIA-H (microhemorrhage in brain parenchyma, superficial siderosis in subarachnoid space)
DWI	Differential diagnosis of cytotoxic edema (including acute infarction)

MRI: magnetic resonance imaging, ARIA: amyloid related imaging abnormalities, FLAIR: fluid attenuated inversion recovery, ARIA-E: amyloid related imaging abnormalities edema/effusion, GRE: gradient-recalled echo, SWI: susceptibility-weighted imaging, ARIA-H: amyloid related imaging abnormalities hemosiderin/hemorrhage, DWI: diffusion-weighted imaging.

in average community-based settings (**Table 7**).[5,18-20,26] The recommended minimum imaging techniques for ARIA evaluation are T2-FLAIR, T2*-GRE, and DWI. T2-FLAIR imaging is essential for detecting ARIA-E, while T2*-GRE (or SWI) is necessary for evaluating ARIA-H. The DWI sequence plays a critical role in distinguishing cytotoxic edema from ARIA-E, such as in cases of acute to subacute cerebral ischemic infarction, and is therefore recommended as part of the basic protocol.

7) ARIA severity classification

In managing ARIA, both symptomatic and radiological severity determine whether to continue, adjust, or discontinue treatment. **Table 8** showed radiological severity of ARIA, which can be classified into mild, moderate, and severe ARIA-E and ARIA-H.[20]

The severity of ARIA-E depends on the location and extent of the abnormality. A FLAIR hyperintensity <5 cm at one location is classified as mild, while a FLAIR hyperintensity of 5–10 cm at one location or <10 cm in two or more locations is considered moderate. A FLAIR hyperintensity >10 cm at one or more locations is classified as severe.

For ARIA-H, severity is assessed based on the number of microhemorrhages or the number of areas with superficial siderosis. Four or fewer (≤4) microhemorrhages or one area of superficial siderosis are considered mild, while 5–9 microhemorrhages or two areas of superficial siderosis are classified as moderate. Ten or more microhemorrhages or three and more areas of superficial siderosis are classified as severe.

8) Differential diagnosis of ARIA

(1) CAA-ri

CAA-ri and ARIA have similar pathophysiology. CAA-ri is an autoimmune encephalopathy caused by autoantibodies targeting Aβ proteins deposited in the walls of cerebral blood vessels, and it is known to be a reversible condition that responds to steroid therapy.[27] The imaging characteristics of CAA-ri are almost identical to those of ARIA-E, making it difficult to distinguish between the two. A key diagnostic point for differentiating CAA-ri from ARIA-E is the presence of underlying CAA (lobar microhemorrhages, superficial siderosis,

Table 8. Radiological severity of ARIA

ARIA type	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

ARIA: amyloid related imaging abnormalities, ARIA-E: amyloid related imaging abnormalities edema/effusion, FLAIR: fluid attenuated inversion recovery, ARIA-H: amyloid related imaging abnormalities hemosiderin/hemorrhage.

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chronic lobar hemorrhage) and whether or not anti-amyloid immunotherapy has been administered.[12,26,27]

(2) ABRA

ABRA is a form of vasculitis that occurs primarily in blood vessels where Aβ has accumulated, characterized by the weakening and damage of the vessel walls due to inflammation (vasculitis) of the vessel wall.[12] Unlike CAA-ri, which exhibits a perivascular inflammatory response confined to the area surrounding the vessels, ABRA is marked by the destruction of the blood vessels and often involves granulomatous inflammation. On MRI, ABRA appears as leptomeningeal enhancement and white matter infiltrative lesions. It typically presents with progressive cognitive decline, headache, seizures, and focal neurological deficits, with lobar hemorrhages being less common than in CAA. While ARIA refers to imaging abnormalities that occur during anti-amyloid immunotherapy, such as edema or hemorrhage due to the removal of Aβ, ABRA can be distinguished by the destructive inflammatory process affecting the blood vessels.

(3) Posterior reversible encephalopathy syndrome (PRES)

ARIA-E and PRES share similar imaging characteristics, including a predilection for the occipital lobe, and both conditions are reversible. However, PRES is often associated with factors such as hypertension, cytotoxic drugs, preeclampsia, sepsis, renal disease, and autoimmune disorders, whereas ARIA occurs following treatment with anti-amyloid immunotherapy, which helps distinguish between the two.[21,26,27]

(4) Ischemic stroke

The FLAIR hyperintensity observed in the brain parenchyma in ARIA-E can appear similar to subacute ischemic stroke. Therefore, to differentiate ischemic stroke, MRI sequences should include DWI, which can help distinguish ischemic stroke with associated cytotoxic edema.[21,26]

(5) Subarachnoid hemorrhage (SAH)

The leptomeningeal FLAIR hyperintensity caused by ARIA-E effusion can appear similar to the imaging of early SAH. SAH is typically accompanied by severe headache, nausea, vomiting, decreased consciousness, and focal neurological signs. To differentiate between acute hemorrhage and ARIA, additional non-contrast CT scans or lumbar punctures may be utilized. ARIA-E effusion often presents as convexity SAH on the cortical surface, which helps distinguish it from typical SAH caused by an aneurysm.[28]

Monitoring, management, and treatment of ARIA

1) Goals of monitoring

The goals of monitoring are: 1) to identify radiological findings of ARIA-E and ARIA-H, 2) to implement enhanced clinical monitoring if symptoms are present, and 3) to perform additional MRI examinations based on clinical judgment.

2) MRI monitoring schedule

The monitoring schedule is recommended not only by the Korean MFDS but also by the U.S. FDA and Japanese MHLW. As shown in **Fig. 4**, it is recommended to confirm the presence or absence of pre-existing ARIA with a recent (within one year) brain MRI before starting treatment. During treatment, MRIs should be performed before the 5th, 7th, and 14th infusions for monitoring. The KDA also recommends conducting MRI scans accordingly. For patients who are *APOE4* carriers or who have confirmed ARIA in previous monitoring, additional monitoring before the 26th infusions should be considered based on the clinician's judgment.

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DND Dementia and Neurocognitive Disorder

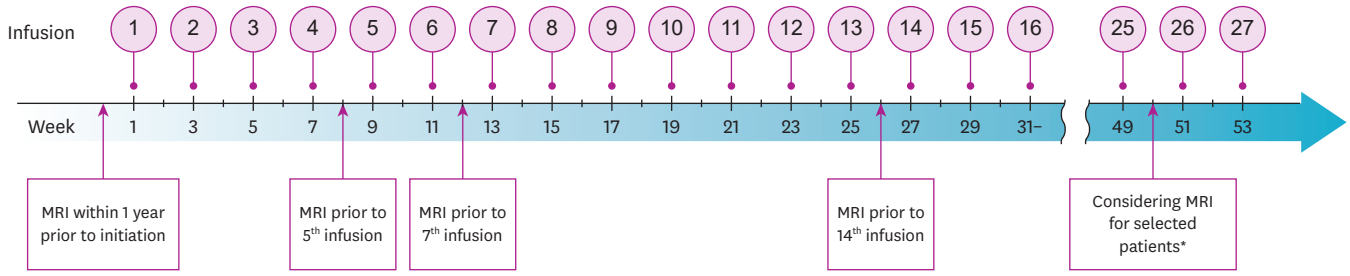

Fig. 4. MRI monitoring schedule. It is recommended to confirm the presence or absence of pre-existing ARIA with a recent (within one year) brain MRI before starting treatment. During treatment, MRIs should be performed before the 5th, 7th, and 14th infusions for monitoring. For patients who are *APOE4* carriers or who have confirmed ARIA in previous monitoring, additional monitoring before the 26th infusions could be considered based on the clinician's judgment. Furthermore, beyond the basic and regular MRI examinations, if suspected ARIA symptoms arise, additional MRI scans can be performed alongside clinical evaluations to assess ARIA.
MRI: magnetic resonance imaging, ARIA: amyloid related imaging abnormalities, *APOE4*: apolipoprotein E ε4 allele.
**APOE4* carriers or those with previous ARIA in previous monitoring.

Furthermore, beyond the basic and regular MRI examinations, if suspected ARIA symptoms arise, additional MRI scans can be performed alongside clinical evaluations to assess ARIA.

3) Symptom monitoring

Since ARIA frequently occurs within the first 14 weeks of starting lecanemab treatment, close observation of the patient's condition is crucial during this period. ARIA-related symptoms may include headache, confusion, visual changes, dizziness, nausea, and gait disturbances (**Table 7**). It is important to monitor for non-specific symptoms (headache, dizziness, nausea) as well as symptoms that overlap with AD (confusion). If symptoms arise, additional safety MRI scans can be performed based on clinical judgment. Special attention should be given to *APOE4* carriers, particularly those who are homozygous.

4) Management and treatment of ARIA

Institutions providing Lecanemab treatment should be adequately prepared to manage severe and serious ARIA. ARIA should be monitored and managed through regular imaging and clinical symptom observation, with readiness for prompt treatment if necessary.

Patients and caregivers should be thoroughly informed in advance about the symptoms indicative of ARIA, and they should be instructed to contact healthcare providers immediately if any suspicious symptoms occur. In particular, since the risk of ARIA may increase when anticoagulants or thrombolytics are administered, additional precautions and risks should be communicated to patients and caregivers prior to the use of these medications. They should also be advised to inform medical personnel about ongoing anti-amyloid immunotherapy during emergency visits.

Clinicians should classify ARIA-E and ARIA-H into mild, moderate, and severe categories based on MRI findings and symptom severity (**Table 8**). Management strategies should be determined based on the radiological severity and clinical symptoms of ARIA, as outlined in **Tables 9** and **10** provided by the Korea MFDS.[4] In cases of severe ARIA-E, initial treatment with high-dose glucocorticoids (e.g., methylprednisolone 1g IV for 5 days) may be considered. If seizures occur, appropriate monitoring and treatment should be implemented as needed.

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Table 9. Recommendations for administration in patients with ARIA-E

Severity of clinical symptoms*	ARIA-E severity on MRI†		
	Mild	Moderate	Severe
Asymptomatic	May continue dosing	Suspend dosing†	Suspend dosing†
Mild	May continue dosing based on clinical judgment	Suspend dosing†	Suspend dosing†
Moderate or severe	Suspend dosing†	Suspend dosing†	Suspend dosing†

ARIA-E: amyloid related imaging abnormalities edema/effusion, MRI: magnetic resonance imaging.
*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.
†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.

Table 10. Recommendations for administration in patients with ARIA-H

Severity of clinical symptoms	ARIA-H severity on MRI		
	Mild	Moderate	Severe
Asymptomatic	May continue dosing	Suspend dosing*	Suspend dosing†
Symptomatic	Suspend dosing*	Suspend dosing*	Suspend dosing†

ARIA-H: amyloid related imaging abnormalities hemosiderin/hemorrhage, MRI: magnetic resonance imaging.
*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.
†Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; use clinical judgment in considering whether to continue treatment or permanently discontinue lecanemab.
‡Radiological stabilization of ARIA-H is defined as the absence of worsening compared to the previous MRI scan where ARIA-H was confirmed.*

DISCUSSION

The KDA has prepared this recommendation to assist in the appropriate use of lecanemab in clinical practice. The summary of the recommendations is as follows:

First, lecanemab is recommended for patients with MCI due to AD and mild AD dementia confirmed to be amyloid biomarker-positive.

Second, lecanemab should be administered in medical institutions that are equipped with the necessary infrastructure and staffed with essential medical personnel who have the expertise required for patient safety.

Third, lecanemab should not be administered to patients with a history of severe hypersensitivity to the drug or to those unable to undergo MRI.

Fourth, it is recommended to perform *APOE* genotyping prior to treatment to predict the risk of ARIA.

Fifth, infusion-related reactions are the most common side effects of lecanemab. Appropriate measures should be taken based on the severity of the symptoms if they occur.

Sixth, ARIA is a relatively common side effect and is usually mild, but it can sometimes cause severe clinical symptoms, so careful administration is recommended. Regular brain MRIs should be conducted to monitor for asymptomatic ARIA during treatment, and if a patient experiences suspected ARIA symptoms, a clinical evaluation, including an additional MRI if necessary, should be performed before continuing lecanemab treatment. In cases of symptomatic ARIA, management should be based on the radiological severity of ARIA and the clinical severity of the symptoms.

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Seventh, the concomitant use of anticoagulants or tPA has been reported to carry a higher risk of serious side effects, such as brain hemorrhage, during the clinical trials of lecanemab. Therefore, if the use of these medications in combination with lecanemab is being considered, additional caution is required.

Eighth, clinicians are recommended to make a comprehensive decision regarding lecanemab administration, taking into account not only its efficacy but also the infrastructure requirements for administration and the risk-benefit ratio as outlined in this recommendation.

Ninth, this recommendation is based on the results of an 18-month phase 3 clinical trial of lecanemab. Therefore, it may be used for up to 18 months in eligible patients. However, the appropriate duration of use should be determined by clinicians after considering efficacy, side effects, and future research findings.

Next, we will review several situations where there is a lack of evidence regarding the therapeutic effects and side effects of lecanemab but which may need to be considered during outpatient care. For the patient groups described below, more in-depth discussions with the patient and their caregivers may be necessary. These scenarios are described with reference to the recommendations from the ADRD-TWG.[5]

First, the efficacy and safety of lecanemab are not known in patients with moderate to severe AD dementia, as these patients were not included in the clinical trials. Therefore, if a patient with mild AD dementia being treated with lecanemab progresses to moderate or severe dementia, there is currently insufficient evidence to recommend whether to continue treatment, based on existing clinical trial results. Until further clinical trial data are available, decisions should be made through discussions with the patient and family members, considering the potential benefits of continued treatment, the observation of disease progression, and the monitoring of ARIA safety.

Second, the participants in the lecanemab clinical trials were primarily patients with late-onset AD. Lecanemab may also be beneficial for patients with early-onset AD (EOAD), which manifests in individuals under the age of 65. However, only 166 out of the total 859 patients treated with lecanemab were between the age of 50 and 64 in the phase 3 clinical trial. Therefore, there might be insufficient information on the safety and efficacy of lecanemab in EOAD patients.

Third, although the majority of patients included in the phase 3 clinical trial of lecanemab were typical early AD patients with memory impairment as the main symptom, patients with atypical AD—such as those with logopenic variant primary progressive aphasia, posterior cortical atrophy, or behavioral/dysexecutive symptoms—were not excluded from the trial if they met the inclusion criteria. However, the safety and efficacy of lecanemab specifically in these atypical AD were not separately reported. Therefore, it is important to inform and discuss with the patient and caregivers that there is limited information regarding lecanemab treatment in atypical AD cases.

Fourth, patients with preclinical AD, who had positive amyloid biomarkers on brain amyloid PET or CSF tests but were cognitively normal based on objective cognitive function tests, were not included in the phase 3 clinical trial of lecanemab. However, ongoing new clinical trials aim to evaluate whether lecanemab treatment can prevent or delay the onset of cognitive symptoms in this patient group.

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This recommendation was developed to provide guidance on selecting appropriate patients who can use lecanemab effectively and safely in the clinical setting in Korea. In the process of creating this recommendation, we referred to existing clinical trial results, prescription information from overseas institutions, and recommendations from the ADRD-TWG, while making efforts to tailor the guidance to the domestic context as much as possible.

Although lecanemab received approval in Korea in May 2024, making it the fourth country in the world to approve the drug, sufficient usage experience has not yet been accumulated. Furthermore, unlike the currently available oral symptomatic drugs of AD, lecanemab is an intravenous infusion with a DMT mechanism, which requires specialized facilities for administration and careful attention to potential side effects. Therefore, when applying the results reported from patients who met the strict inclusion/exclusion criteria of clinical trials to real-world clinical patients, there may be differences in efficacy and side effects.

For this reason, the need for a registry to systematically accumulate real-world data on drug use has been raised. In the United States, where lecanemab was first approved, the Alzheimer's Association established a registry, known as the Alzheimer's Network for Treatment and Diagnostics, to collect real-world data not only for lecanemab but also for newly approved treatments in the future. Similarly, the KDA is preparing the Korean Joint Registry for Alzheimer's Treatment and Diagnostics (JOY-ALZ) with the same objective. JOY-ALZ will collect data on new AD treatments and diagnostic technologies approved in Korea and applied to real-world clinical patients. Through this registry, we are expecting to accumulate a wide range of data that cannot be obtained from clinical trials, such as long-term treatment effects, side effects, drug discontinuation or resumption, and cost-effectiveness. It is also anticipated that the registry would provide practical evidence for AD patients in Korea, based on the real-world application of the newly developed AD treatment. After the sufficient experience with lecanemab is accumulated in clinical setting in the future, the KDA plans to publish a revised recommendation reflecting this information.

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SUPPLEMENTARY MATERIAL

Supplementary File 1
Korean version

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