

SUPPLEMENTARY MATERIAL

This supplement material is an English translation of 'Amyloid-related Imaging Abnormalites (ARIA) in the Era of Anti-Amyloid Beta Monoclonal Antibodies: Recent Updates for the Radiologist' article for non-Korean readers. When citing this supplement, the original article ([J Korean Soc Radiol 2025;86\(1\):17-33; https://doi.org/10.3348/jksr.2024.0140](https://doi.org/10.3348/jksr.2024.0140)) must be cited in order to respect the rights of the authors and the journal's citation score.

Amyloid-related Imaging Abnormalites (ARIA) in the Era of Anti-Amyloid Beta Monoclonal Antibodies: Recent Updates for the Radiologist

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Lecanemab and donanemab have received full U.S. Food and Drug Administration (FDA) approval, and subsequently, lecanemab has been approved by the Korean FDA and it has recently entered commercial use in Korea. This has increased interest in anti-amyloid immunotherapy for Alzheimer's disease. Anti-amyloid immunotherapy has shown potential to modify the progression of the disease by specifically binding to amyloid β , a key pathological product in Alzheimer's disease, and eliminating accumulated amyloid plaques in the brain. However, this treatment can be accompanied by a side-effect, amyloid-related imaging abnormalities (ARIA), which requires periodic monitoring by MRI. It is crucial to detect ARIA and accurately assess the severity by radiology. The role of the radiologist is important in this context, requiring proficiency in basic knowledge of ARIA, and in diagnosing/evaluating ARIA. This review comprehensively addresses ARIA, covering its definition, pathophysiology, incidence, risk factors, radiologic assessment of severity, differential diagnosis, and management strategies.

Index terms Alzheimer Disease; Dementia; Immunotherapy

INTRODUCTION

Alzheimer's disease is a degenerative disease of the brain that has become a primary social and medical concern worldwide, particularly with the acceleration of the aging population. Until recently, treatment for Alzheimer's disease was extremely limited, providing only symptomatic improvement, including mediation such as acetylcholinesterase inhibitors and NMDA

receptor antagonist. However, in June 2021, aducanumab had received conditional approval from the U.S. Food and Drug Administration (FDA) as the first anti-amyloid β immunotherapeutic agent, and a new era of Alzheimer's disease therapy began. Following aducanumab, lecanemab received full FDA approval on July 6, 2023, and donanemab received full FDA approval on July 2, 2024. In Korea, lecanemab was approved by the Korean FDA on May 24, 2024, and became commercially available domestically in December 2024.

The core pathological mechanism of Alzheimer's disease is amyloid plaque deposition in the brain parenchyma and cerebral vessel walls (1). Deposition of amyloid plaques is believed to occur at an early stage of Alzheimer's disease pathophysiology, triggering a subsequent cascade of tau phosphorylation, neurofibrillary tangle formation, and microglial activation, ultimately leading to neurodegeneration and progressive cognitive decline (2-4). Anti-amyloid β immunotherapeutic agents were developed on the premise that targeting amyloid β —the main component of amyloid plaques—can remove accumulated amyloid plaques in the brain, halting further plaque deposition and the resulting pathophysiological cascade (2). This anti-amyloid β immunotherapy demonstrated potential in clinical trials to slow disease progression by reducing amyloid plaques burden in the brain. However, amyloid-related imaging abnormalities (ARIA) has been commonly reported as a main adverse effect in this anti-amyloid β immunotherapy (5). Because ARIA can affect subsequent anti-amyloid β immunotherapy—such as whether to continue therapy, adjust the dose, or terminate treatment—patients receiving anti-amyloid β immunotherapy must undergo periodic MRI monitoring. In particular, radiologists play a critical and irreplaceable role in the early detection and accurate grading of ARIA severity. Hence, it is crucial to have an accurate understanding of ARIA's definition, etiology, imaging features, severity grading, and management in the context of the latest anti-amyloid β immunotherapies.

This review provides a comprehensive overview of ARIA that encompasses fundamental concepts, such as its definition, pathophysiology, imaging findings, and recent updates related to anti-amyloid β immunotherapy for Alzheimer's disease.

OVERVIEW OF ARIA

DEFINITION OF ARIA

During clinical trials of anti-amyloid β immunotherapies, treatment-emergent MRI signal abnormalities were commonly reported. In 2010, the Alzheimer's Association Research Roundtable first addressed these MRI abnormalities, established associated recommendations, and coined the term 'Amyloid-Related Imaging Abnormalities (ARIA)' (5). ARIA is subdivided into ARIA-E and ARIA-H. The 'E' in ARIA-E stands for edema or effusion, whereas the 'H' in ARIA-H represents microhemorrhage and superficial siderosis. In ARIA-E, the edema and effusion are caused by extravasated proteinaceous fluid that manifests as vasogenic edema in the brain parenchyma or sulcal effusion, represented as high signal intensity on fluid-attenuated inversion recovery (FLAIR) images. ARIA-E can appear in either white or gray matter (or both) and may involve gyral swelling. ARIA-E most frequently occurs in the occipital lobe, followed by the parietal, frontal, and temporal lobes. ARIA-E is generally transient and usually resolves within 3–4 months. ARIA-H, on the other hand, results from the leakage of heme prod-

ucts and presents as microhemorrhages (≤ 10 mm) in the parenchyma or superficial siderosis in the subarachnoid or pia mater space, detectable by T2* gradient echo (GRE) or susceptibility-weighted imaging (SWI). Both ARIA-E and ARIA-H tend to occur early in the course of anti-amyloid β immunotherapy.

PATHOPHYSIOLOGY OF ARIA

ARIA is diagnosed based on MRI findings, and the exact pathophysiological mechanisms of ARIA have not been fully elucidated. One prevailing hypothesis involves the interplay between cerebral amyloid angiopathy (CAA) and administration of anti-amyloid β immunotherapeutic agents. Under normal physiological conditions, some amyloid plaques are cleared via perivascular pathways and cerebral blood vessels. However, in Alzheimer's disease, amyloid plaques accumulate in cerebral vessel walls, damaging these perivascular clearance routes and exacerbating amyloid plaque deposition. A recent study found that 96.3% of Alzheimer's disease cases demonstrate pathological evidence of CAA (6). CAA is characterized by amyloid plaque—primarily A β 40—accumulation in the walls of meningeal arteries, cerebral arteries, and arterioles. Age and the presence of the ApoE $\epsilon 4$ gene are known risk factors for more extensive deposition of amyloid β in the vascular walls. CAA reduces both vascular stability and perivascular clearance, and this predisposes patients to spontaneous microhemorrhages. When anti-amyloid monoclonal antibodies bind to amyloid β in the brain parenchyma and cerebrovascular walls, the subsequent movement and clearance of amyloid via perivascular pathways are increased, imposing an additional burden on these routes (7). This congestion can temporarily exacerbate amyloid β deposition in arterial walls while triggering an antibody-mediated inflammatory response in the cerebral vessel walls, compromising vessel integrity and blood-brain barrier function. Consequently, proteinaceous fluid and red blood cell or their breakdown products can leak into the brain parenchyma or meningeal spaces, leading to ARIA-E (edema or effusion) or ARIA-H (microhemorrhage or superficial siderosis) (5, 7).

INCIDENCE OF ARIA

A meta-analysis of Phase II and III randomized clinical trials published before 2022 reported overall incidences of 6.5% for ARIA-E and 7.8% for ARIA-H in patients receiving anti-amyloid β immunotherapies (8). However, more recent Phase III trials indicate higher incidences, ranging from 12.6%–25.1% for ARIA-E and 7.4%–31.4% for ARIA-H (9-14). Incidence rates also vary somewhat by drug. In Phase III lecanemab trials, ARIA-E and ARIA-H occurred in 12.6% and 16.9% of patients, respectively, with any ARIA incidence at 21.5% (11, 14). Donanemab demonstrated ARIA-E in 24.0%, ARIA-H in 31.4%, and any ARIA in 36.8%, a generally higher rate than lecanemab (15). Notably, a subgroup analysis in a Phase III lecanemab trial reported that ARIA-E incidence was lower in East Asian participants compared to the overall study population (6.5% vs. 12.6%) (16). Despite a high overall incidence, most ARIA cases remain asymptomatic, with symptomatic ARIA reported in 2.8% of patients for lecanemab and 17.9% for donanemab (11, 14, 15).

Differences in incidence of ARIA across anti-amyloid β immunotherapies likely reflect variations in how each monoclonal antibody binds to specific subtypes of amyloid β (monomers, oligomers, protofibrils, or fibrils). Lecanemab targets amyloid β protofibrils during

plaque formation, whereas donanemab targets oligomers and protofibrils (17).

RISK FACTORS FOR ARIA

Clinical trials and related studies on anti-amyloid β immunotherapy have identified several risk factors for ARIA, including drug dose, ApoE $\epsilon 4$ status, and microhemorrhage on baseline MRI (5, 18-20). A dose-dependent relationship has been demonstrated, with higher doses correlating with increased ARIA incidence in Phase II trials that assigned different doses to separate patient groups and Phase III aducanumab studies (19).

Multiple studies found higher ARIA incidence in ApoE $\epsilon 4$ carriers than non-carriers, with the highest incidence in homozygote carriers. For instance, in a Phase III lecanemab trial, ARIA-E incidence was 32.6% in homozygotes, 10.9% in heterozygotes, and 5.4% in non-carriers; ARIA-H incidence was 14.0% in homozygotes, 10.9% in heterozygotes, and 5.4% in non-carriers (11, 14, 15). Similarly, in Phase III donanemab trial, ARIA-E occurred in 40.6% of homozygotes, 22.8% of heterozygotes, and 15.7% of non-carriers.

Patients exhibiting typical MRI findings of CAA prior to therapy—such as intracerebral microhemorrhages or superficial siderosis—are also at higher risk of ARIA. Thus, clinical trials of anti-amyloid β immunotherapy excluded patients with five or more baseline microhemorrhages or any superficial siderosis (21). In routine clinical practice, evaluating ApoE $\epsilon 4$ status and carefully scrutinizing baseline MRI for microhemorrhages or superficial siderosis can help predict the risk of ARIA. For those at elevated risk of ARIA, more frequent MRI monitoring is recommended, and physicians should thoroughly discuss these risks with patients and their caregivers.

CLINICAL SYMPTOMS OF ARIA

Most ARIA cases are asymptomatic. When there are symptoms, they are typically transient, mild, and reversible. Reported symptoms varied, ranging from nonspecific neurological complaints (headache, nausea, vomiting) to confusion and gait or visual disturbances. In rare but in severe cases, cerebral edema, seizures, or even death were reported. Hospitalization or intensive care may be required, and misdiagnosis as ischemic stroke is possible. Therefore, newly developed neurological symptoms in patients receiving anti-amyloid β immunotherapy require careful evaluation. Symptomatic ARIA-E was reported as 2.8% in Phase III lecanemab trial and 17.9% in Phase III donanemab trial, with 8.8% and 8.3% of these symptomatic cases deemed severe (11, 14, 15).

IMAGING FEATURES OF ARIA

This review primarily focuses on the radiological aspects of ARIA. For details on appropriate MRI protocols for ARIA monitoring in Korea such as essential MR sequences, scan parameters, recommended timing and conditions for MRI, and critical factors for interpretation refer to “Expert Recommendations for a Standard MRI Protocol to Detect Amyloid-Related Imaging Abnormalities from Anti-Amyloid Monoclonal Antibody Therapy in Alzheimer’s Disease” (22).

SEVERITY OF ARIA

ARIA severity is the key factor in deciding whether to continue treatment, adjust dosage, or discontinue anti-amyloid β immunotherapy. This, accurate, objective evaluation of ARIA severity on MRI is crucial (23, 24). Several scales have been proposed, including the Barkhof Grand Total Scale and the 3-point/5-point Severity Scales of ARIA-E (SSAE-3, SSAE-5) (25-28). The FDA guidelines assess the severity of ARIA by categorizing ARIA-E, ARIA-H microhemorrhage type, and ARIA-H superficial siderosis type each into mild, moderate, or severe categories (Table 1) (29).

ARIA-E severity is determined by lesion size and number (Figs. 1-3). A single FLAIR hyperintensity lesion smaller than 5 cm is graded as mild (Fig. 1), one site measuring between 5

Table 1. Severity of ARIA by Radiology

ARIA Type	Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity (brain parenchyma or sulcus) One location <5 cm	FLAIR hyperintensity (brain parenchyma or sulcus) 5-10 cm in single greatest dimension, or more than 1 site of involvement, each measuring <10 cm	FLAIR hyperintensity (brain parenchyma or sulcus) >10 cm with associated gyral swelling and sulcal effacement
ARIA-H (microhemorrhage)	\leq 4 new microhemorrhages	5 to 9 new microhemorrhages	10 or more new 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, FLAIR = fluid-attenuated inversion recovery

Table 2. Management of ARIA Depending on the Severity of Symptoms and the Severity of Radiographic ARIA-E or ARIA-H on MRI

Symptom Description			
No Symptoms		Mild Symptoms	Moderate or Severe
ARIA-E on MRI			
Mild	May continue dosing	May continue dosing based on clinical judgment	Suspend dosing*
Moderate	Suspend dosing*	Suspend dosing*	Suspend dosing*
Severe	Suspend dosing*	Suspend dosing*	Suspend dosing*
No Symptoms		Any Symptoms	
ARIA-H on MRI			
Mild	May continue dosing	Suspend dosing†	
Moderate	Suspend dosing†	Suspend dosing†	
Severe	Suspend dosing§	Suspend dosing§	

Mild symptoms; discomfort noted; no disruption of daily activity, Moderate symptoms; discomfort sufficient to reduce or affect normal daily activity, Severe symptoms; 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.

†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.

‡Radiological stabilization of ARIA-H is defined as the absence of worsening compared to the previous MRI scan where ARIA-H was confirmed.

§Suspend until MRI demonstrates radiographic stabilization‡ and symptoms, if present, resolve; use clinical judgment in considering whether to continue treatment or permanently discontinue lecanemab.

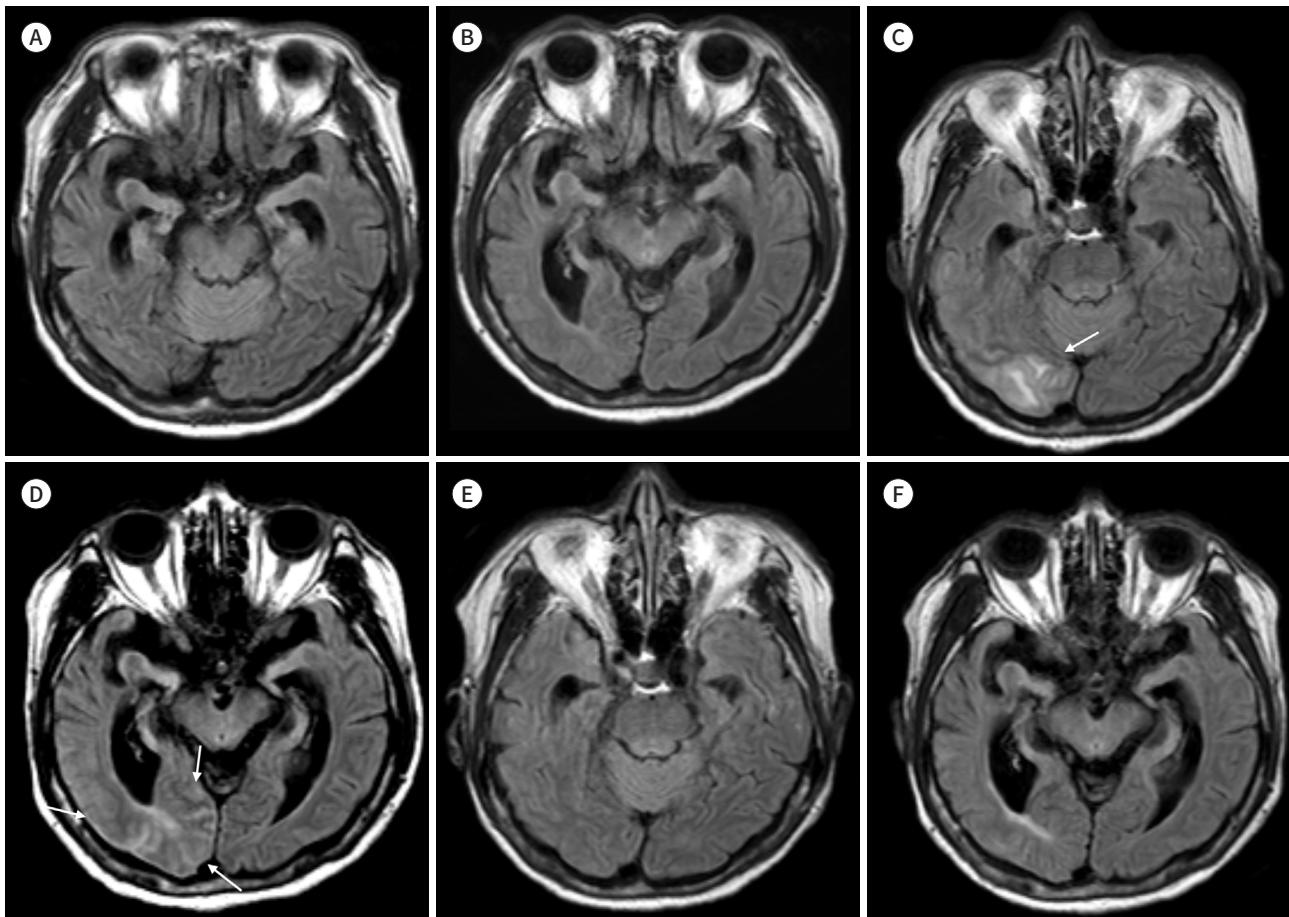
ARIA = amyloid-related imaging abnormalities

Fig. 1. ARIA-E in a 75-year-old female patient, an ApoE ϵ 4 homozygote carrier, undergoing aducanumab therapy.

A, B. On her baseline MRI, there was a mild degree of white matter hyperintensity. Three months later, she complained of a headache. **C, D.** On follow-up MRI, there is FLAIR high signal intensity edema with sulcal effusion in the right occipital area, suggestive of ARIA-E (arrows). The MRI shows hyperintensities with an extent measuring <5 cm, which is classified as mild ARIA-E. She is suspended from the aducanumab therapy and her symptoms gradually resolved.

E, F. Two months after suspension of the infusion, ARIA-E is resolved on a follow-up MRI.

ARIA = amyloid-related imaging abnormalities, FLAIR = fluid-attenuated inversion recovery



and 10 cm or multiple (≥ 2) lesions, each measuring up to 10 cm, is graded as moderate (Figs. 2, 3), and any lesion larger than 10 cm is graded as severe (Fig. 2 in reference [23]). ARIA-H severity is separately evaluated for microhemorrhages and superficial siderosis based on their number or extent (Figs. 3, 4). Fewer than four microhemorrhages or one superficial siderosis region is graded as mild, five to nine microhemorrhages or two superficial siderosis regions is graded as moderate, and ten or more microhemorrhages or over two superficial siderosis regions is graded as severe.

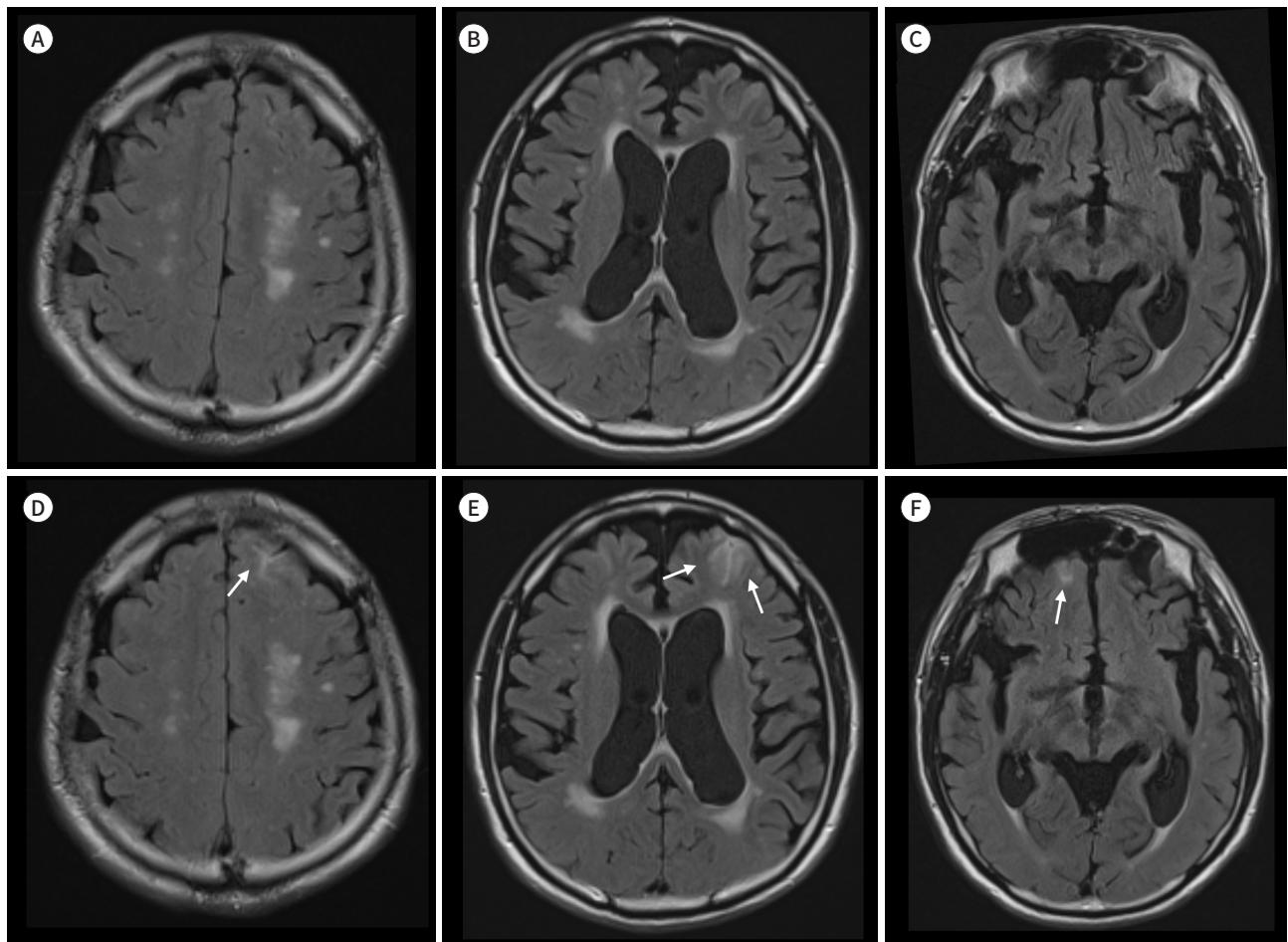
For measurements of ARIA-E extent, any longest axis (axial, coronal, or sagittal) is measured, including the parenchymal lesion and associated edema, sulcal effusion, or sulcal hyperintensity on FLAIR. Typically, measuring in the acquired imaging plane is sufficient; however, if a lesion extends significantly in the craniocaudal direction, coronal measurements or estimating lesion size by slice count multiplied by slice thickness should be considered. If separate lesions are demarcated by normal parenchyma or normal sulci, they should be

Fig. 2. ARIA-E in a 75-year-old male patient, an ApoE ε4 heterozygote carrier, undergoing lecanemab therapy.

A-C. On his baseline MRI, there is a moderate degree of white matter hyperintensity.

D-F. Nine weeks later, surveillance MRI shows sulcal FLAIR high signal intensity and brain parenchymal FLAIR high signal intensity in the left frontal and right frontal areas, suggestive of ARIA-E (arrows). The patient was asymptomatic. Three regions and an extent measuring <5 cm would be classified as moderate.

ARIA = amyloid-related imaging abnormalities, FLAIR = fluid-attenuated inversion recovery



counted and measured individually. A lesion crossing multiple lobes is classified as a single lesion if contiguous, but if they cross hemispheres, each side should be measured separately without spanning the midline. Compared to the baseline MRI, the cumulative number of newly developed microhemorrhages and superficial siderosis areas is counted for evaluation of ARIA-H severity. The number of microhemorrhages found on baseline MRI prior to treatment is not included in severity assessment of ARIA-H after treatment initiation. Patients with superficial siderosis on baseline MRI are excluded from the treatment (30). Regarding the microhemorrhages, depending on the specific exclusion criteria, patients with up to 4 or 9 microhemorrhages on their baseline MRI may be allowed to receive treatment (30).

CO-OCCURRENCE OF ARIA-E AND ARIA-H

Because ARIA-E and ARIA-H share a fundamental mechanism involving decreased vascular integrity and increased permeability, leakage of proteinaceous fluid or red blood cell (or

Fig. 3. Concurrent ARIA-E and ARIA-H in a 69-year-old male patient with mild cognitive impairment undergoing aducanumab therapy.

A, B. On his baseline MRI, there is a mild degree of white matter hyperintensity.

C, D. On his baseline GRE sequence, there are three hemorrhages (arrows) at the right parietal lobe and bilateral cerebellum.

E, F. On follow-up MRI after five months, FLAIR high signal intensity edema with sulcal effusion (arrows) with an extent measuring >5 cm was noted in the right parietal area, suggestive of moderate ARIA-E (arrows) without symptoms.

G, H. In addition, on the GRE sequence, superficial siderosis (arrows) suggestive of mild ARIA-H was observed in the right parietal area, where the ARIA-E had developed. The patient voluntarily discontinued the medication.

ARIA = amyloid-related imaging abnormalities, GRE = gradient-recalled echo, FLAIR = fluid-attenuated inversion recovery

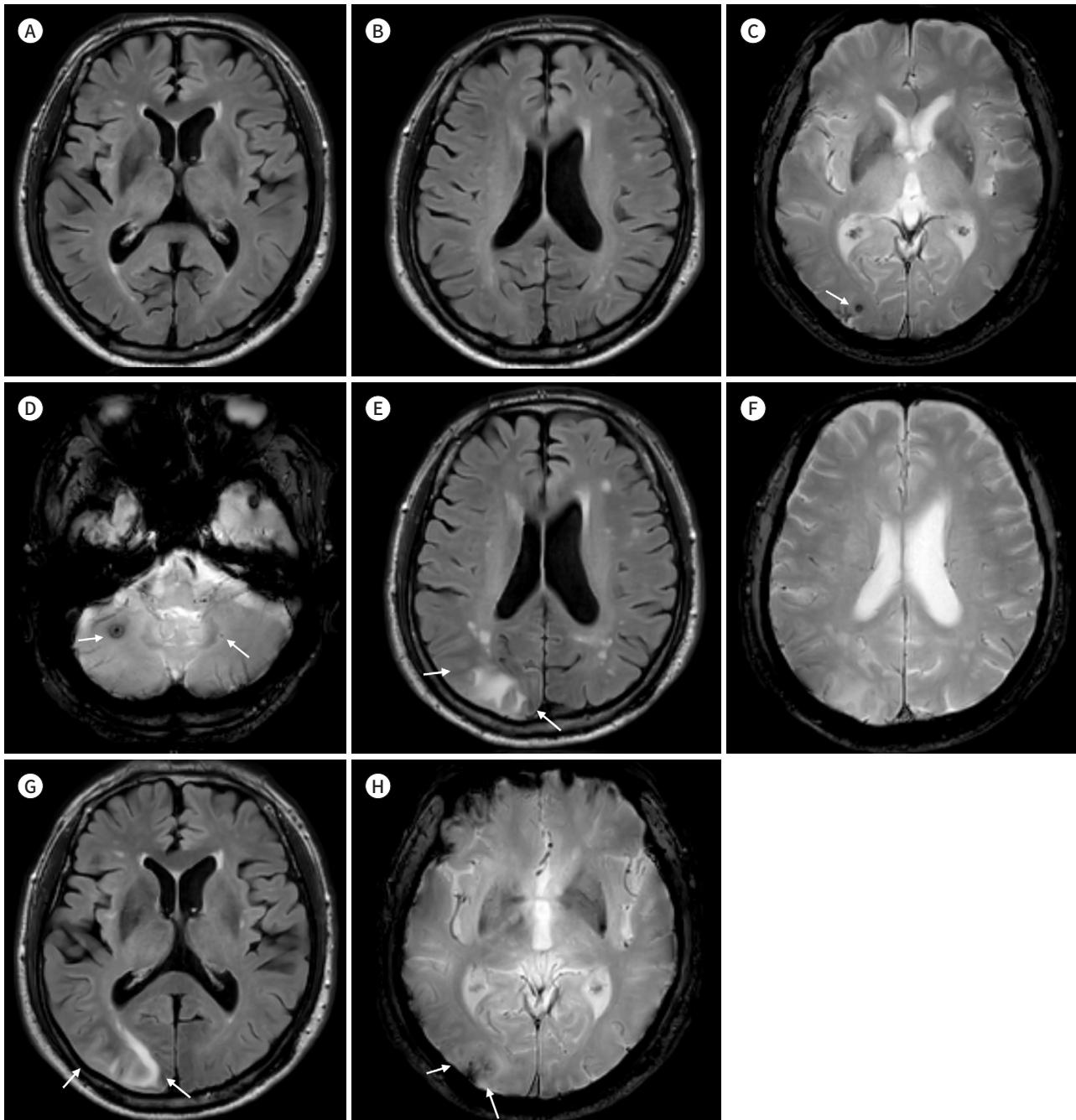
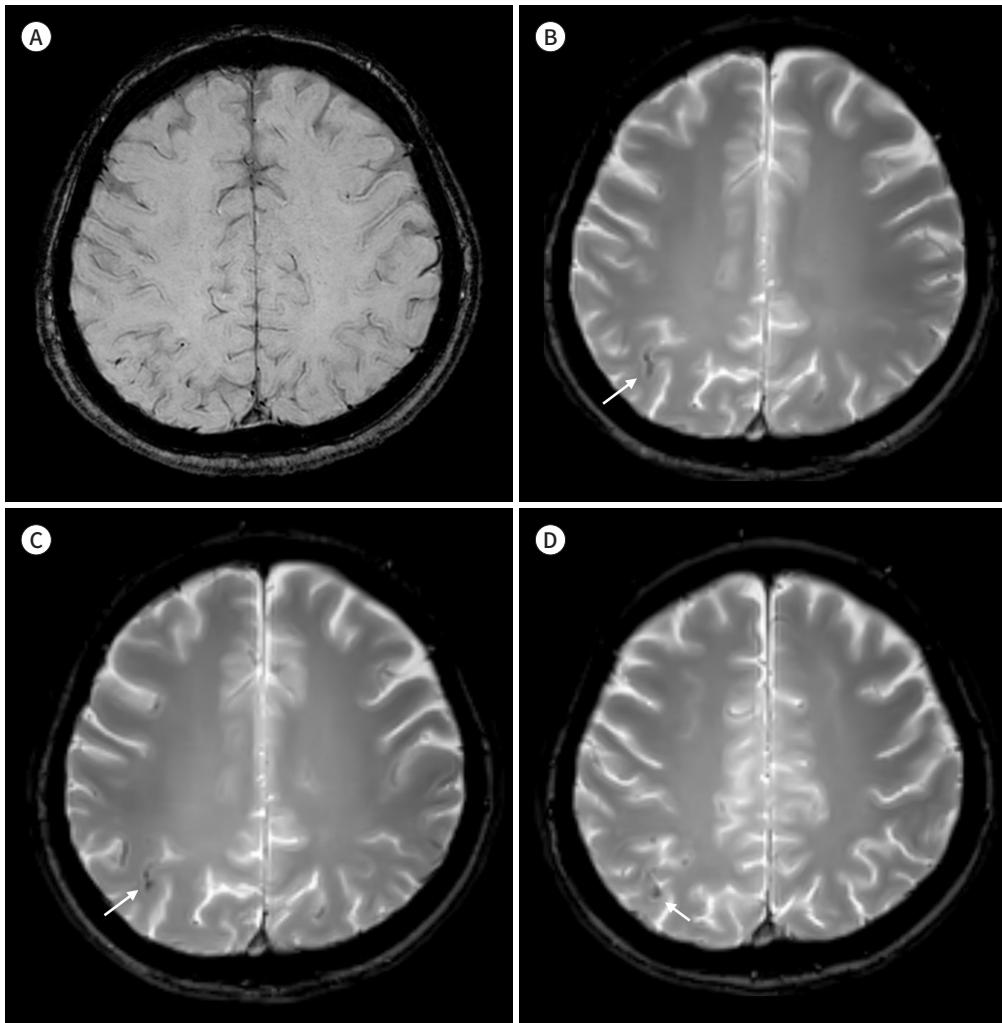


Fig. 4. ARIA-H in a 58-year-old female patient with mild cognitive impairment, an ApoE ϵ 4 non-carrier, undergoing lecanemab therapy.

- A. On her baseline MRI, there are no microhemorrhages or superficial siderosis.
- B. On follow-up MRI after three months, SWI shows superficial siderosis at the right parietal sulci (arrow) without symptoms, which is classified as mild ARIA-H (superficial siderosis). She had no associated symptoms.
- C, D. On follow-up MRI after six months, SWI shows additional two microhemorrhages (arrows) at the right parietal lobe, which is classified as mild ARIA-H (microhemorrhage).

ARIA = amyloid-related imaging abnormalities, SWI = susceptibility weighted imaging



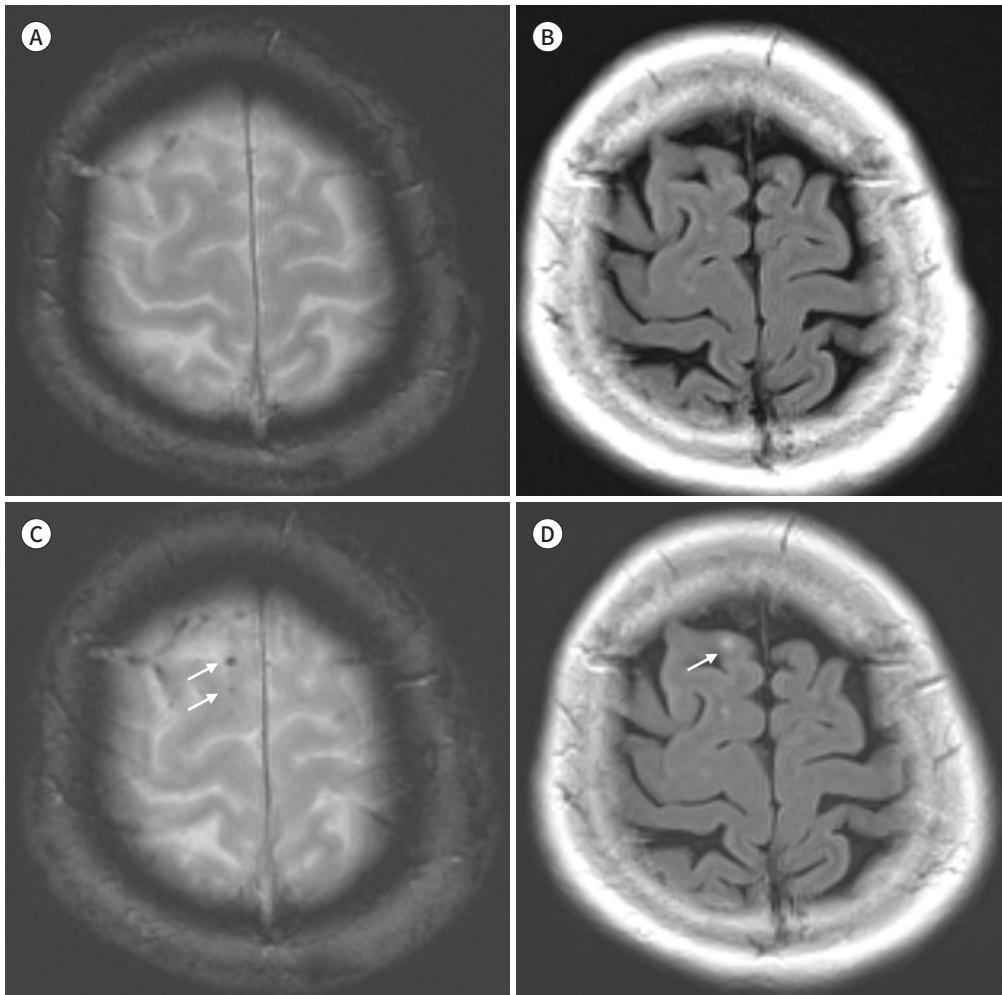
their breakdown products) commonly occurs in tandem (Figs. 3, 5) (19). In a bapineuzumab clinical trial, approximately 50% of ARIA-H cases either occurred concurrently with ARIA-E or shortly before or after ARIA-E onset (31). In a Phase III gantenerumab trial, 13.5% of patients exhibited both ARIA-E and ARIA-H simultaneously (9). In many instances, new ARIA-H emerges in the same location as earlier ARIA-E or appears after ARIA-E resolution (Fig. 3). While ARIA-E usually resolves over a few weeks to months, ARIA-H (microhemorrhages and superficial siderosis) may persist or only partially fade (19, 30). Therefore, if ARIA-H is detected, careful evaluation of the corresponding FLAIR images for subtle ARIA-E is warranted. Conversely, ARIA-E can occur without ARIA-H if red blood cell or their heme products have not yet leaked—or insufficient time has elapsed for the breakdown products to influence T2*

Fig. 5. ARIA-E in a 70-year-old female patient with mild cognitive impairment, an ApoE ε4 homozygote carrier, undergoing lecanemab therapy.

A, B. On her baseline MRI, there is no remarkable microhemorrhage nor white matter hyperintensity.

C, D. Eleven months later, surveillance MRI shows new two microhemorrhages and focal (<5-cm extent) brain parenchymal FLAIR high signal intensity in the right frontal area, suggestive of ARIA-E (arrows). The patient was asymptomatic. A single region and an extent measuring <5 cm, and two new microhemorrhages would be classified as mild ARIA-E and mild ARIA-H.

ARIA = amyloid-related imaging abnormalities, FLAIR = fluid-attenuated inversion recovery



signals. Differences in the imaging time relative to the onset of vascular leakage may also account for instances when ARIA-E and ARIA-H in the same location are identified at different time points (29).

DIFFERENTIAL DIAGNOSIS OF ARIA

CAA-RELATED INFLAMMATION (CAA-RI)

CAA-related inflammation (CAA-RI) is pathophysiologically related to ARIA. In acute or subacute CAA-RI, cerebrospinal fluid can transiently show elevated levels of anti-amyloid β autoantibodies, returning to typical levels observed in patients with noninflammatory CAA

or AD once clinical symptoms and imaging abnormalities resolve (32, 33). Based on such findings, CAA-RI in patients with AD who are not receiving anti-amyloid β immunotherapy and CAA may be interpreted as spontaneous ARIA-E in, whereas ARIA-E in the setting of anti-amyloid β immunotherapy is viewed as an iatrogenic CAA-RI or CAA-RI-like syndrome. Solopova et al. (34) reported autopsy findings of an acute arteritis pattern resembling severe CAA-RI in a fatal ARIA case under lecanemab treatment, including widespread inflammation with macrophages and activated microglia, along with arteriol degeneration (25, 34). Unlike drug-induced ARIA, spontaneous CAA-RI is an autoimmune process that responds to immunosuppressive therapy and corticosteroids (35). On contrast enhanced MRI, involving the meninges or brain parenchyma may be enhancing (36, 37) in conjunction with cortical/subcortical microhemorrhages, superficial siderosis, or chronic lobar hemorrhage, typical features of CAA. Distinguishing CAA-RI from ARIA-E solely by imaging is difficult, so medication history whether the patient is on anti-amyloid β immunotherapy is crucial (23, 35, 38).

ISCHEMIC STROKE

Because ARIA often presents with nonspecific neurological symptoms, it may be mistaken for ischemic strokes. Additionally, FLAIR hyperintensity in ARIA-E can resemble acute or subacute infarction. However, ARIA-E represents vasogenic edema and thus does not exhibit diffusion restriction on diffusion-weighted imaging (DWI). Consequently, including DWI sequence in MRI protocols for ARIA monitoring is advised to rule out the cytotoxic edema associated with acute ischemic stroke (23, 26).

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES)

Both ARIA-E and posterior reversible encephalopathy syndrome (PRES) frequently involve the occipital lobe and exhibit similar FLAIR hyperintensities, and both are generally reversible. PRES is associated with identifiable risk factors such as uncontrolled hypertension, cytotoxic agents, preeclampsia, sepsis, renal disease, or autoimmune disorders. In contrast, ARIA arises specifically in the context of anti-amyloid β immunotherapy (22, 25, 34). Hence, integrating relevant clinical information, including underlying risk factors, is essential for accurate diagnosis.

SUBARACHNOID HEMORRHAGE (SAH)

Sulcal effusion in ARIA-E appears as a hyperintense signal in the cortical sulci on FLAIR, potentially mimicking early subarachnoid hemorrhage (SAH) (23, 26). However, SAH often presents with severe symptoms, such as decreased consciousness and focal neurological deficits. Noncontrast CT or lumbar puncture can help distinguish acute hemorrhage from ARIA. In cases where SAH occurs in a patient on anti-amyloid β immunotherapy without a clear cause (e.g., aneurysmal rupture or trauma), spontaneous subarachnoid bleeding may represent ARIA-H. Thus, vascular imaging, skull fracture evaluation, and assessment for parenchymal trauma are needed to exclude other etiologies. Additionally, ARIA-E effusion typically appears as a convexity-type SAH, differentiating it from typical SAH due to a ruptured aneurysm (39).

USE OF ARTIFICIAL INTELLIGENCE FOR ARIA DETECTION AND ASSESSMENT

Diagnosis of ARIA primarily depends on imaging findings, and subsequent treatment strategy rely on imaging-based severity assessments. Therefore, early detection and objective grading of ARIA severity on MRI are imperative. Baseline MRI evaluation is also critical for determining eligibility or exclusion before initiating anti-amyloid β immunotherapy. Various AI-based software tools for image detection and quantitative measurement focusing on MRI have been introduced (40). In the context of anti-amyloid β immunotherapy, several software solutions also have been developed to detect and quantify microhemorrhages at baseline and during safety monitoring and grade microhemorrhage and ARIA-E automatically.

NeuroQuant® ARIA by Cortechs.ai, received FDA 510(k) clearance in September 2024. This deep learning-based tool analyzes two-dimensional and three-dimensional FLAIR along with T2* GRE or SWI sequences to quantify ARIA-E and ARIA-H. It generates a severity score and also compares serial images over time. Another software, Icobrain aria by Icometrix, which also quantifies ARIA-E and ARIA-H severity scores, received FDA 510(k) clearance in November 2024 and is approved in Europe and Japan. Tested in an aducanumab clinical trial, Ico-brain aria helped radiologists detect ARIA more accurately (41). The area under the curve for radiologists assisted by Icobrain aria ranged from 0.83 to 0.87, and sensitivity was higher in the software-assisted group (41). Neurophet has also developed AQUA AD software which quantifies ARIA, receiving Korean FDA approval in December 2024.

As baseline and monitoring MRI scans are repeated multiple times for patient selection and safety monitoring in anti-amyloid β immunotherapy, AI-based software may prove increasingly beneficial for identifying appropriate candidates, detecting ARIA, and assessing its severity. Further validation and multidisciplinary studies will be essential to ensure the reliability of these AI solutions in clinical practice.

TREATMENT OF ARIA

MANAGEMENT AND THERAPY OF ARIA

Management strategies for ARIA in anti-amyloid β immunotherapy have evolved over time. Early trials mandated permanent treatment discontinuation or temporary suspension (until resolution) upon any detection of ARIA, regardless of symptomatic status (42-44). However, subsequent studies revealed that continuing treatment with close monitoring in asymptomatic or mildly symptomatic cases did not lead to worse ARIA-E severity outcomes compared to patients whose therapy was discontinued (45).

Currently, recommended ARIA management involves periodic MRI assessments and careful monitoring for clinical symptoms. For example, guidelines from the Korean Dementia Association on lecanemab advise classifying ARIA-E and ARIA-H as mild, moderate, or severe based on MRI findings and clinical symptoms (Table 1), then applying the management strategies outlined in Table 2 (21, 46). In asymptomatic patients with mild ARIA-E or ARIA-H on imaging, therapy may be continued. ARIA-E, which is both radiologically mild and has mild clinical symptoms can also be managed with ongoing treatment under physician judgment. However, in cases of radiologically moderate or severe ARIA-E or in patients presenting moderate to severe clinical symptoms (i.e., symptoms that interfere with or prevent normal daily

activities), treatment should be halted. Treatment can be resumed once imaging findings resolve or improve and any clinical symptoms have abated, based on physician judgment. For ARIA-H, treatment should be interrupted if imaging shows moderate or severe changes or if any symptoms are present. Once imaging stabilizes (i.e., no further deterioration compared to previous scans) and symptoms have resolved, treatment can be resumed at the physician's discretion. In instances of severe ARIA-H on imaging, permanent discontinuation may be considered. These recommendations are intended as guidance; actual clinical decisions on whether to continue, discontinue, or resume therapy depend on physician's judgment.

CONCLUSION

Anti-amyloid β immunotherapies have opened a new era in the treatment of Alzheimer's disease. However, these treatments carry the risk of ARIA, which necessitates multiple brain MRI assessments before and during treatment to ensure patient safety. Accurate baseline MRI evaluation is crucial when selecting appropriate candidates. Because the management plan of whether to continue, adjust, or halt treatment hinges on the presence and severity of ARIA, prompt detection and careful severity grading on monitoring MRIs is paramount. Accordingly, radiologists play a pivotal role in diagnosing and evaluating ARIA. A firm grasp of ARIA's fundamental concepts, identification high-risk patients pre-therapy, precise monitoring during treatment, and efficient communication with clinicians are all essential for optimizing patient outcomes.

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