Molecular Imaging CRO Network

Micron's ViewPoint

Safety Evaluation of Anti-Amyloid-β Antibodies in Alzheimer's Disease: ARIA

Micron, Inc.

Contents

Introduction

Dementia is a neurodegenerative disease in which cognitive function deteriorates due to organic damage in the brain, resulting in difficulties in daily life and social activities.[1] Alzheimer's disease (AD) accounts for the largest proportion (67%)[2] of all dementias, and it is estimated that the number of AD patients will increase to 4-6 million by 2030.[3] In June 2021, the U.S. Food and Drug Administration (FDA) approved Aducanumab as a new medication for AD,[4] and in January 2023 gave expedited approval of Lecanemab.[5] In Japan, both drugs have not been approved as of the time of this writing (March 2023), but in January 2023, Eisai Co. announced that it had submitted an application to the Pharmaceuticals and Medical Devices Agency (PMDA) for manufacturing and marketing approval of Lecanemab.[6]

Aducanumab and Lecanemab are human monoclonal antibodies that selectively bind to and remove from the brain the neurotoxic amyloid-β (Aβ) protofibrils which are considered to be one of the factors that cause AD.[6] Existing drugs for AD are symptom-modifying agents that temporarily improve symptoms but do not alter the underlying disease process. In contrast, Aducanumab and Lecanemab are disease-modifying agents that act on the mechanism of AD onset and improve pathology and condition,[7] and are expected to provide a fundamental treatment for AD.

While anti-Aβ antibodies such as these drugs are expected to be effective in AD patients, the safety profile of these drugs may be compromised by adverse events known as amyloid-related imaging abnormalities (ARIA). ARIA is classified into ARIA-E and ARIA-H. ARIA-E is characterized by findings of cerebral edema or effusions, and ARIA-H as those of cerebral microhemorrhages or superficial siderosis on MRI images (*Figure 1*). In Phase III trials of Lecanemab, ARIA-E and ARIA-H were identified in 12.6% and 17.3% of patients, respectively,[8] requiring careful monitoring of patient safety. The U.S. Prescribing Information (USPI) for Lecanemab recommends that the decision to continue or discontinue the drug for patients with ARIA-E or ARIA-H findings should be based on the severity detected by both MRI imaging and clinical symptoms.[9] Early detection and differentiation of ARIA on MRI imaging and at follow-up are important for patient safety. However, ARIA imaging evaluation has not been widely adopted in clinical practice, and physicians with sufficient education and experience are limited. This paper provides an overview of ARIA, including a summary of ARIA imaging evaluation in clinical trials related to anti-Aβ antibodies.

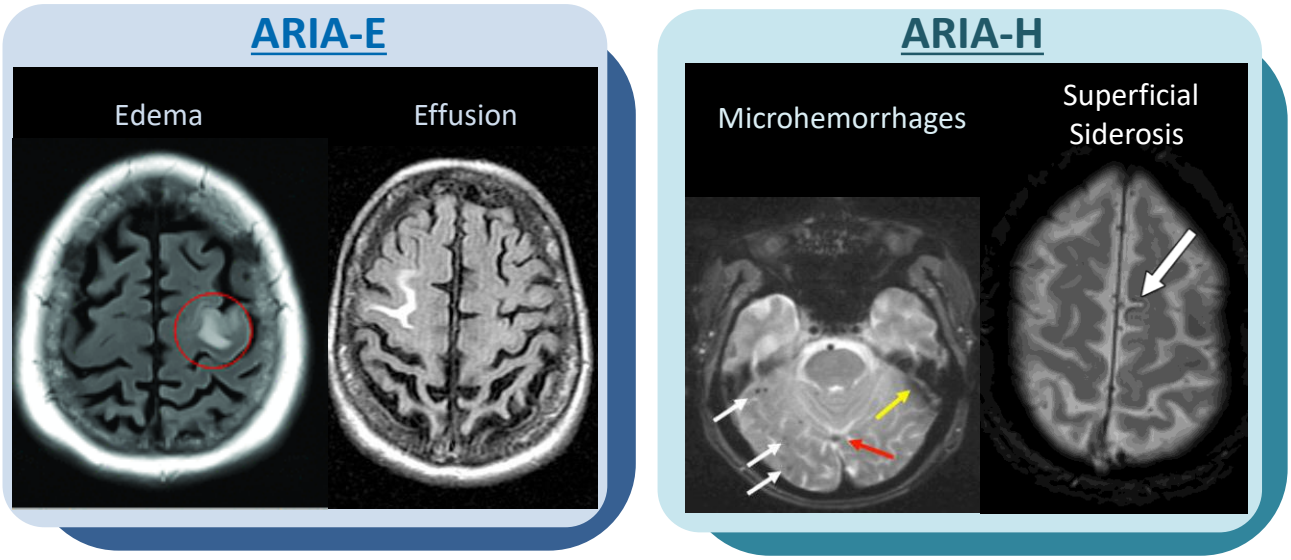

Figure 1. *MRI Images of ARIA-E and ARIA-H*[10-12]

ARIA Overview

History

- Vasogenic edema and cerebral microhemorrhages were first observed in MRI images of some subjects in phase II clinical trials of anti-Aβ antibody Bapineuzumab.[13-16]
- In July 2010, the Alzheimer's Association Research Roundtable workgroup (AARR) introduced the term "ARIA" to describe MRI findings in AD patients on anti-Aβ antibody therapy.[12]
- ARIA has also been reported in clinical trials of anti-Aβ antibodies such as Gantenerumab, Donanemab, Aducanumab, and Lecanemab.[9,17-19]

Pathomechanism (Hypothesis)

- ARIA occurs due to binding of monoclonal antibodies to accumulated Aβ in the cerebral parenchyma and vasculature. This binding leads to amyloid clearance, resulting in loss of vessel wall integrity and vessel leakage of proteinaceous fluid (ARIA-E) and heme products (ARIA-H).[10-12,20]

Types

ARIA-E

- Hyperintensity in Fluid Attenuated Inversion Recovery (FLAIR) images centered on the parenchyma of the parietal, occipital, and frontal lobes (edema).[10-12,20]
- Signal high-intensity seen on FLAIR images in the parenchyma (effusion).[10-12,20]

ARIA-H

- Round, hypointense lesions less than 10 mm in diameter observed in the cerebral parenchyma in Gradient Echo (GRE) or Susceptibility Weighting Imaging (SWI) (microhemorrhages).[10-12,20]
- Curvilinear hypointense areas observed in GRE or SWI in the parenchyma (superficial siderosis).[10-12,20]

Symptoms

- Most patients who develop ARIA with anti-Aβ antibody therapy are asymptomatic.[10-12,20]
- Symptoms tend to be transient in most cases, typically occurring early in the course of treatment, with the risk decreasing later in treatment.[10-12,20]
- ARIA-E and ARIA-H may occur together.[8]
- Symptoms include headache, confusion, dizziness, nausea, gait disturbance, rare convulsions, and status epilepticus.[9-12,20]
- May be severe and life-threatening, requiring hospitalization and specific treatment (admission to intensive care unit, electroencephalography, corticosteroids, antiepileptic medications, etc.).[10,20]

Risk Factors

- Apolipoprotein E (ApoE) ε4 carriers (especially ApoE ε4 homozygotes)[10-12,20]
- Baseline microbleeding[10-12,20]
- Concomitant use of antithrombotic medications[10-12,20] (ARIA-H)
- Dose-dependent on anti-Aβ antibodies (ARIA-E)[10-12,20]

Differential Diagnosis

- Ischemic stroke (ARIA-E edema)[10-12,20]
- Subarachnoid hemorrhage (ARIA-E effusion)[10-12,20]
- Posterior Reversible Encephalopathy Syndrome (PRES)[10-12,20] (ARIA-E)
- Cerebral amyloid angiopathy[10-12,20]

ARIA in Clinical Trials of Anti-Aβ Antibodies

The Alzheimer's Association Research Roundtable workgroup recommends detecting ARIA early in treatment and monitoring progress regularly in clinical trials of anti-Aβ antibodies.[12] Many clinical trials of anti-Aβ antibodies have been conducted since the early 2000s, and the incidence of ARIA-E and ARIA-H is summarized below from the confirmed studies[8,17-24] (*Table 1*). It should be noted that the results of the studies cannot be directly compared due to differences in the anti-Aβ antibodies or their study designs.

The incidence of both ARIA-E and ARIA-H varies widely, which may be related to differences in the binding sites of anti-Aβ antibodies (N-terminus, C-terminus, etc.) and binding affinity to Aβ structures (aggregated, soluble type, etc.).[10-11,20]

Some clinical trials analyze ARIA by subpopulation, such as ApoEε4 carriers/non-carriers, allele type (heterozygous/homozygous), concordance, monogenicity, etc. For more details, please refer to published papers of clinical trial results.

Anti-Aβ Antibody	Study Title	Dosage	ClinicalTrials.gov ID	ARIA-E	ARIA-H		
						Microhemorrhages	Superficial Siderosis
Bapineuzumab	-	0.5 mg/kg	NCT00574132 NCT00575055	ApoEε4 carriers 4.2% (14/314) ApoEε4 non-carriers 15.3% (103/658)	None	None	None
Solanezumab	EXPEDITION1 EXPEDITION2	400 mg	NCT02642432 NCT02738138	0.6% (13/2052)	5.2% (107/2052)	None	None
Gantenerumab	Scarlet Road	225 mg	NCT01224106	13.5% (35/260)	16.2% (42/260)	None	None
Crenezumab	CREAD	60 mg/kg	NCT02353598	0.0% (0/21)	4.7% (1/21)	None	None
Donanemab	TRAILBLAZER-ALZ	700 mg	NCT03367403	27.5% (36/131)	30.5% (40/131)	19.8% (26/131)	17.6% (23/131)
Aducanumab	EMERGE ENGAGE	10 mg/kg	NCT02484547 NCT02477800	35.0% (362/1029)	28.3% (291/1029)	19.1% (197/1029)	14.6% (151/1029)
Lecanemab	Clarity AD	10 mg/kg	NCT03887455	12.6% (113/898)	17.3% (155/898)	14% (126/898)	5.60% (50/898)

Table 1. *Incidence of ARIA-E and ARIA-H in Clinical Trials of Anti-Aβ Antibodies*

MRI Imaging of ARIA

The Alzheimer's Association Research Roundtable workgroup published a recommended MRI imaging protocol for ARIA detection in clinical trials of anti-Aβ antibodies.[12] Wherever possible, efforts should be made to ensure that the following MRI parameters are consistent and the same MRI scanner is used from study entry through treatment.

Magnetic Field Strength — 3T (recommended), 1.5T (minimum)

- High field strength scanners have greater sensitivity and are recommended, but due to limited availability at sites, 1.5T scanners can be used as a minimum standard.[11-12]
- The use of higher field strength MRI scanners to detect ARIA-H must be balanced against the clinical importance of the ARIA-H findings.[11-12]

Slice Thickness — 5 mm or less

- Thinner slices increase resolution but decrease signal to noise ratio (SNR), so a balance is required.[11-12]
- Thicker slices may make it difficult to distinguish ARIA-H microhemorrhages from vascular flow voids.[11-12]

TE — More than 20 ms (GRE)

- Longer TE improves detection, but lowers SNR, so a balance is required.[11-12]

Sequence

ARIA-E	:FLAIR
ARIA-H	:GRE or SWI
common	:DWI

- FLAIR is used to detect ARIA-E. GRE or SWI is used to detect ARIA-H.[11-12]
- If ARIA findings are present, DWI will be used to rule out cytotoxic edema.[11-12]
- High-resolution 3D-FLAIR can more clearly delineate parenchymal edema changes in ARIA-E and reduce cerebrospinal fluid (CSF) artifacts, but 2D-FLAIR can be used if 3D-FLAIR is not available at the site.[11]
- 3D-GRE can reduce partial volume effects, however MRIs that can use 3D-GRE are limited.[11]
- SWI provides better detection of microhemorrhages, but due to limited availability at sites and large differences between MRI scanners, GRE has been used to detect ARIA-H in most clinical trials to date.[11]
- MPRAGE and volumetric analysis may be performed at patient enrollment in clinical trials of AD patients, but are not required for safety monitoring of ARIA during anti-Aβ antibody treatment.[11]
- Turbo spin echo (TSE) or fast spin echo (FSE) can be used to help resolve ambiguous T2* findings, such as differentiating microhemorrhages from vascular flow voids.[11]
- Contrast imaging is not recommended unless there is a dilemma with diagnosis or incidental findings require further evaluation.[11]

Imaging Findings of ARIA-E

ARIA-E is characterized by an increased signal on FLAIR sequences that represents edema, effusion, or exudate, with the absence of other signs of cytotoxic edema such as diffusion limitation (*Figure 2*). ARIA-E may be associated with locoregional mass effect or gyral swelling, most commonly in the occipital lobe, followed by the parietal, frontal, and temporal lobe, and rarely in the cerebellum.[10-12] Parenchymal signal abnormalities can be quite subtle in a single region but may be multi-focal or nearly pan-hemispheric.[11-12] The increased MR signal is primarily seen in what appears to be the leptomeningeal space. This leptomeningeal involvement may be seen in isolation or near associated grey matter alterations.[12]

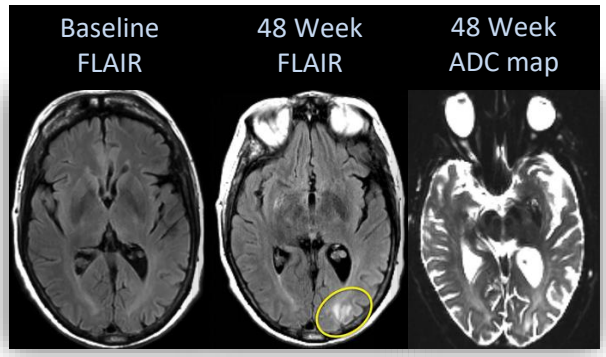

Figure 2. *Imaging Findings of ARIA-E[10]*

- 60-year-old AD patient on anti-Aβ antibody therapy
- FLAIR images at 48 weeks after therapy show increased signal with associated gyral swelling involving left occipital (oval) and right frontal (oval) lobes.
- ADC map shows no corresponding restricted diffusion, suggesting cytotoxic edema. These findings are consistent with ARIA-E, which is characterized by edema and effusion.

Shading artifacts (*Figure 3-A*), vendor variations (*Figure 3-B*), oxygen supplementation (*Figure 3-C*), poor CSF suppression (*Figure 3-D*), and magnetic artifacts such as hearing aids (*Figure 3-E*) result in high FLAIR signals, making ARIA-E detection more difficult.[11] It is difficult to differentiate posterior reversible encephalopathy syndrome (PRES), ischemic stroke, and subarachnoid hemorrhage.[10-12,20] Although the imaging features of these conditions overlap with ARIA, the clinical history and presence or absence of clinical symptoms may provide information to distinguish them from ARIA.

It is important to compare baseline FLAIR images for ARIA-E detection and images during anti-Aβ antibody treatment. If the ARIA-E is subtle or occurs in a particularly peripheral pattern, it may be evaluated by careful comparison with the baseline FLAIR images.[11] Subtraction images comparing the difference between baseline and MRI images during treatment may contribute to the detection of minute ARIA-E.[25]

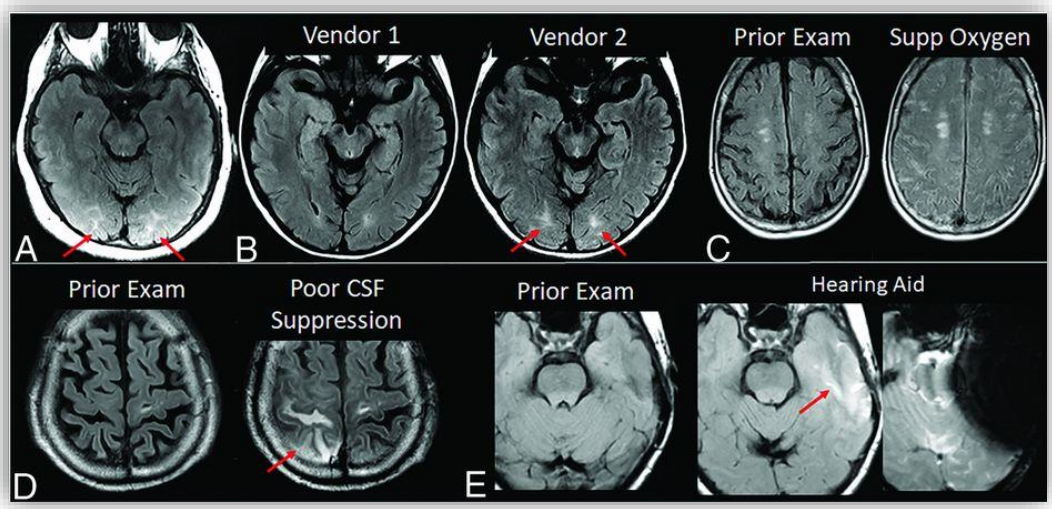

Figure 3. *Imaging Findings that Mimic ARIA-E*

Imaging Findings of ARIA-H

ARIA-H is characterized by the presence of hemosiderin, a blood degradation product, that manifests as parenchymal microhemorrhages. Microhemorrhages are defined as hypointense rounded foci less than 10cm in diameter on GRE and SWI (*Figure 4*). Leakage of heme products into the leptomeningeal or subpial space results in superficial siderosis, which manifests as curvilinear hypointensity along the brain surface. These MRI findings parallel a lobar or peripheral predilection that often occurs at the gray-white matter junction or cortex, etc..[10-12,20] This appearance is in contrast to microhemorrhages due to hypertensive causes, which typically involve the deep gray matter, cerebellar hemispheres, and brainstem.[10-11]

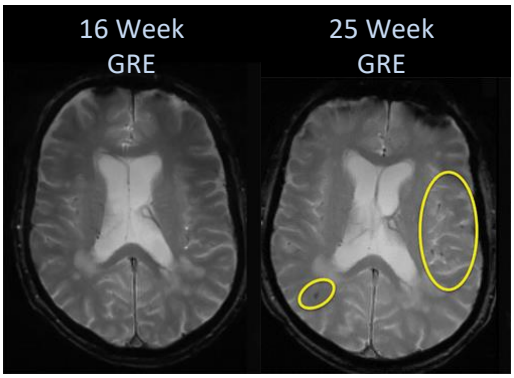

Figure 4. *Imaging Findings of ARIA-H[10]*

- 67-year-old AD patient on anti-Aβ antibody therapy
- At least 5 microhemorrhages (ovals) in the right parietal lobe and left frontal lobe.

Motion and partial volume effects result in poor visualization of a previously documented right frontal microhemorrhage[11] (*Figure 5-A*). Areas of prominent air-tissue susceptibility effects may induce punctate artifacts that look similar to microhemorrhages, especially near the frontal sinuses, mastoid air cells and skull base. The vessel may mimic a microhemorrhage on a single section but can be traced as a vessel flow void on adjacent slices[11] (*Figure 5-B*). T2-weighted images can be useful for comparison, as flow voids in vessels do not have a blooming effect.[11] Susceptibility-related signal loss from physiologic mineralization in the basal ganglia may be misinterpreted as microhemorrhages and should not be incorporated into the overall microhemorrhage count[11] (*Figure 5-C*). Bulk susceptibility effects may prevent evaluation of the inferior temporal lobes[11] (*Figure 5-D*).

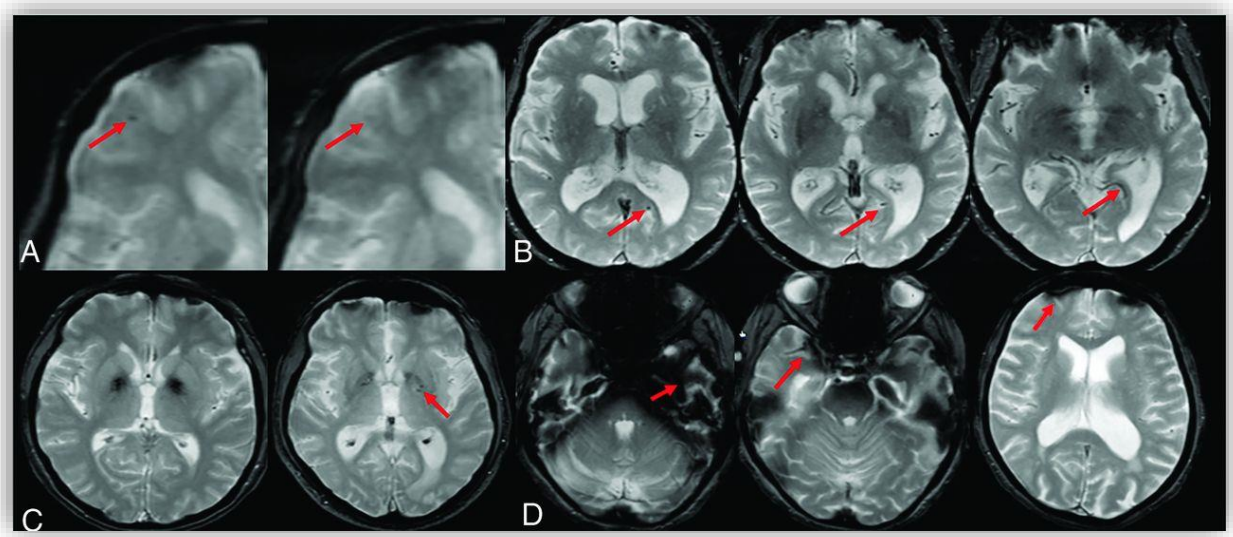

Figure 5. *Imaging Findings that Mimic ARIA-H*

Classification of ARIA Severity on Imaging

Appropriate classification of the severity assessment of ARIA on imaging is important for patient safety monitoring, as the decision to discontinue/continue dosing is made according to a combination of severity assessment and clinical assessment in the US prescribing information for Lecanemab.[9] The severity ratings used in clinical trials are presented below.

Barkhof Grand Total Scale (BGTS)

The Barkhof Grand Total Scale (BGTS) is a visual rating scale with a maximum score of 60 that assesses ARIA-E in six regions of the left and right brain (12 regions in total).[26] For each region, parenchyma, sulcal, and swelling are scored on a 0-5 scale, and the highest score for each region is summed.

0. No abnormalities
1. Single lesion ≤ 2 cm
2. Multiple lesions ≤ 2 cm
3. Lesion >2 cm but <4 cm
4. Lesion ≥4 cm
5. Entire lobe

Region		Parenchymal	Sulcal	Swelling	Highest Score Per Region
Frontal lobe	Right	0-5	0-5	0-5	0-5
	Left	0-5	0-5	0-5	0-5
Parietal lobe	Right	0-5	0-5	0-5	0-5
	Left	0-5	0-5	0-5	0-5
Temporal lobe	Right	0-5	0-5	0-5	0-5
	Left	0-5	0-5	0-5	0-5
Occipital lobe	Right	0-5	0-5	0-5	0-5
	Left	0-5	0-5	0-5	0-5
Central	Right	0-5	0-5	0-5	0-5
	Left	0-5	0-5	0-5	0-5
Infratentorial	Right	0-5	0-5	0-5	0-5
	Left	0-5	0-5	0-5	0-5
Total Score					0-60

ARIA-E Extent	ARIA-E Focality	SSAE-3	SSAE-5
<5 cm	Monofocal	1 (Mild)	1 (Mild)
	Multifocal	2 (Moderate)	2 (Mild+)
5-10 cm	Monofocal		3 (Moderate)
	Multifocal		4 (Moderate+)
>10 cm	Monofocal	3 (Severe)	5 (Severe)
	Multifocal		

3-point Severity Scale of ARIA-E (SSAE-3)
5-point Severity Scale of ARIA-E (SSAE-5)

The SSAE-3 and SSAE-5 are visual rating scales that rate ARIA-E on a 3-point and 5-point scale based upon a single linear measurement of the largest area of lesion.[10-11,27-28]

- If there are lesions in both hemispheres, they should be reported as separate locations, since measurements would not cross the midline.
- Each lesion which is physically separate (e.g., separated by normal brain tissue, sulci, and gyri) should be measured separately.
- If the lesion spans multiple contiguous brain lobes, it should still be counted as a single location.

3-point Severity Scale of ARIA-H

A visual rating scale for ARIA-H rates the number of microhemorrhages and the number of areas of superficial siderosis.[10-11] Microhemorrhages and superficial siderosis are scored using the cumulative number of treatment-emergent microhemorrhages. The number of microhemorrhages before treatment are not counted in the ARIA-H severity grading.[11]

	Mild	Moderate	Severe
Microhemorrhages	≤4 locations	5-9 locations	≥10 locations
Superficial Siderosis	1 focal area	2 focal areas	3 or more areas

Central Review of ARIA

When ARIA findings are observed in clinical trials of anti-Aβ antibodies, prompt evaluation is essential to determine dose adjustment or treatment discontinuation. However, ARIA-E cases are often asymptomatic and can manifest as rather subtle alterations in MR signal, which can be overlooked.[12] In a phase II trial of Bapineuzumab, approximately 40% (15/36) of asymptomatic ARIA-E were missed by the local radiologists[29-30] suggesting that detection and differentiation of ARIA is limited to radiologists with expertise in the field.

In clinical trials, there are two reading methods for evaluating the safety of ARIA: the site reading method, in which radiologists at each site read the data, and the central review method, in which a small number of radiologists with expertise in ARIA read the data (*Figure 6*). Central review has the advantage of facilitating accurate evaluation of ARIA by multiple independent readers and increasing inter-reader reliability since only a small number of readers evaluate ARIA throughout the study. Consistent training for readers can also provide uniformity for recognizing ARIA. The Alzheimer's Association Research Roundtable workgroup also mentioned the usefulness of central review in clinical trials of anti-Aβ antibodies,[12] and the FDA-approved Lecanemab also uses central review for ARIA in all patients.[8]

Central review of ARIA primarily involves severity classification using the ARIA-E and ARIA-H visual rating scales. BGTS was used to evaluate ARIA-E in the phase II study of Bapineuzumab[27] and SSAE-3 was used for Solanezumab, Donanemab, Aducanumab, and Lecanemab.[10-11,27-28] Other evaluation scales should be used according to study design, feasibility, and required analysis information.

In order to quickly assess the presence and severity of ARIA, MRI images should be transferred to the central review without delay, images should be read quickly, and assessment results should be sent back to the sites. To create this system requires the cooperation of sites, secure networks, and a smooth environment where readers can quickly read the data. This means support is needed from experienced and skilled central review team members. Reading designs for safety evaluation include a single reader or a 2+1 reading model, as well as a method in which multiple readers are pooled to allow rapid evaluation, with image data assigned to the available readers.[31]

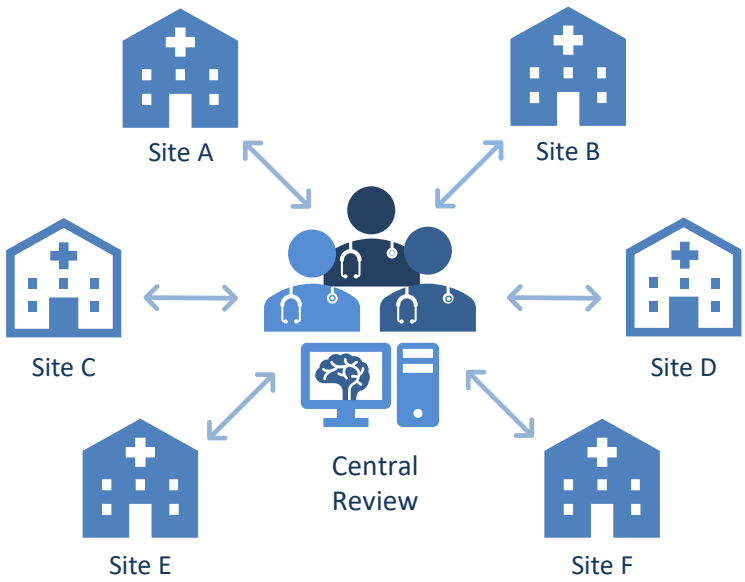

Figure 6. *Schematic of Central Review*

Conclusion

In today's aging society a fundamental treatment for AD is desired, so the advent of anti-Aβ antibodies represented by Aducanumab and Lecanemab is expected to improve the therapeutic environment and quality of life for AD patients. As the number of AD patients taking anti-Aβ antibodies increases, the number of AD patients who develop ARIA, a side effect, is also expected to increase in the future. Therefore, clinical sites treating AD patients and companies developing anti-Aβ antibodies for clinical trials need to be familiar with MRI imaging conditions and findings to detect and differentiate ARIA. This article provides an overview of ARIA, including clinical trials of anti-Aβ antibodies, imaging findings of ARIA, severity classification, recommended MRI imaging conditions, and central review of ARIA. With the anticipated regulatory approval of anti-Aβ antibodies in Japan, we hope that this paper will contribute to a better understanding of ARIA, which has not yet been made fully aware in clinical practice. Detailed pathomechanisms, risk factors, optimal imaging conditions for each MRI scanner, and clinical data on ARIA will be updated with the results of clinical trials of anti-Aβ antibodies under development and the accumulation of various data in actual clinical practice.

Micron is a contract research organization (imaging CRO) that supports imaging-based clinical trials and clinical research. We have experience supporting the central review for the safety assessment of ARIA-E and ARIA-H in AD clinical trials. We also have an extensive network of radiologists specialized in MRI imaging of the central nervous system (CNS) field and Key Opinion Leaders (KOL) in clinical trials for AD.

IRUM ® neo, the reading system developed by Micron, can generate assessment reports in line with individual clinical trials and can create the assessment format for ARIA severity classification as described in this paper. A detailed description of IRUM ® neo can be found on Micron's website.
(https://micron-kobe.com/archives/works_en/video_irumneo_and_i-boarding)

Micron has also signed a business alliance agreement with Icometrix (Belgium), a leading company in brain image analysis software that utilizes AI technology, which can provide the latest MRI image analysis technology to the medical field. A detailed description of Icometrix can be found on their website. (https://icometrix.com)

For general inquiries, questions about training, or consultation regarding central review of clinical trials for AD, please contact us at the following address.

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Business Details

1. Support for development of pharmaceuticals, diagnostics, medical devices (saMD), and biomarkers using imaging technology
2. Clinical development support (monitoring, quality control, imaging core lab work, image analysis, reading support, etc.)
3. Support for investigational GMP manufacturing of PET medications
4. Consulting for clinical development

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References

1. Government of Japan Public Relations Online. "The Basics of Dementia You Need to Know". https://www.gov-online.go.jp/useful/article/201308/1.html
2. Asada T. "Prevalence of Dementia in Urban Areas and Response to Impairment of Life Functioning of Dementia". https://www.tsukuba-psychiatry.com/wp-content/uploads/2013/06/H24Report_Part1.pdf
3. Ninomiya T, Kiyohara H, Obara T, Yonemoto K. "Study on Future Estimation of the Elderly Population with Dementia in Japan". https://mhlw-grants.niph.go.jp/system/files/2014/141031/201405037A/201405037A0001.pdf
4. FDA News Release, FDA, Jun 7, 2021, "Grants Accelerated Approval for Alzheimer's Medication". https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-medication
5. FDA News Release, FDA, Jan 6, 2023, "FDA Grants Accelerated Approval for Alzheimer's Disease Treatment". https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-disease-treatment
6. Eisai Co. "Eisai Receives Priority Review Status in Japan for Lecanemab, an Anti-Amyloid-Beta Protofibril Antibody". https://www.eisai.co.jp/news/2023/news202312.html
7. Iwatsubo T. "Lecanemab and Future Dementia Treatment". https://www.youtube.com/watch?v=FpBkz0dwy08
8. Van Dyck CH, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med 2023; 388:9-21.
9. Eisai Inc. "LEQEMBI - lecanemab injection, solution". https://xn--dailymed-x53g0h4974d.nlm.nih.gov/dailymed/fda/fdamedicationXsl.cfm?setid=9d1ff 786-e577-410a-a273-c4d7d0e4e975&type=display
10. Roytman M, et al. Amyloid-Related Imaging Abnormalities: An Update. AJR Am J Roentgenol. 2023 Feb 8; 1-13.
11. Cogswell PM, Barakos JA, Barkhof F, et al. Amyloid-related imaging abnormalities with emerging Alzheimer disease therapeutics: Detection and reporting recommendations for clinical practice. AJNR 2022; 43:e19-e35.
12. Sperling RA, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: Recommendations from the Alzheimer's Association Research Roundtable Workgroup. Alzheimers Dement. 2011 Jul; 7(4):367-85.
13. Black RS, Sperling RA, Safirstein B, Motter RN, Pallay A, Nichols A, et al. A single ascending dose study of bapineuzumab in patients with Alzheimer. Alzheimer Dis Assoc Disord. 2010 Apr-Jun; 24(2):198-203.
14. Salloway S, Sperling R, Gilman S, et al; Bapineuzumab 201 Clinical Trial Investigators. A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. Neurology 2009; 73:2061-2070.
15. Sperling R, Salloway S, Fox N, Barackos J, Morris K, Francis G, et al. Risk Factors and Clinical Course Associated with Vasogenic Edema in a Phase II Trial of Bapineuzumab. American Academy of Neurology; Seattle, Washington: 2009.
16. Arrighi HM, Barakos J, Barkhof F, et al. Amyloid-related imaging abnormalities-haemosiderin (ARIA-H) in patients with Alzheimer's disease treated with bapineuzumab: a historical, prospective secondary analysis. J Neurol Neurosurg Psychiatry 2016; 87:106-112.
17. Ostrowitzki S, Lasser RA, Dorflinger E, et al. Scarlet Road Investigators. A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. Alzheimers Res Ther 2017; 9:95.
18. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in early Alzheimer's disease. N Engl J Med 2021; 384:1691-1704.
19. Salloway S, Chalkias S, Barkhof F, et al. Amyloid-related imaging abnormalities in two phase 3 studies evaluating aducanumab in patients with early Alzheimer disease. JAMA Neurol 2022; 79:13-21.
20. Barakos J, Purcell D, Suhy J, et al. Detection and Management of Amyloid-Related Imaging Abnormalities in Patients with Alzheimer's Disease Treated with Anti-Amyloid Beta Therapy. J Prev Alzheimers Dis 2022; 9:211-220.

21. Salloway S, Sperling RA, Fox NC, Blennow K, Klunk W, Raskind M, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med 2014; 370:322-333.

22. Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med 2014; 370:311-321.

23. Guthrie H, Honig LS, Lin H, et al. Safety, tolerability, and pharmacokinetics of crenezumab in patients with mild-to-moderate Alzheimer's s disease treated with escalating doses for up to 133 weeks. J Alzheimers Dis 2020; 76:967-79.

24. Haeberlein SB, Aisen PS, Barkhof F, et al. Two randomized phase 3 studies of aducanumab in early Alzheimer's disease. J Prev Alzheimers Dis 2022; 9:197-210.

25. Martens RM, et al. The value of subtraction MRI in the detection of amyloid-related imaging abnormalities with oedema or effusion in Alzheimer's patients: An interobserver study. Eur Radiol. 2018 Mar; 28(3):1215-1226.

26. Barkhof F, Daams M, Scheltens P, et al. An MRI rating scale for amyloid-related imaging abnormalities with edema or effusion. AJNR 2013; 34:1550-1555.

27. Bechten A, Wattjes MP, Purcell DD, Aliaga ES, Daams M, Brashear HR, et al. Validation of an MRI rating scale for amyloid-related imaging abnormalities. J Neuroimaging 2017; 27:318-325.

28. Klein G, et al. Comparing ARIA-E severity scales and effects of treatment management thresholds. Alzheimers Dement (Amst). 2022 Dec 2; 14(1):e12376.

29. Sperling R, Salloway S, Brooks DJ, et al. Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: A retrospective analysis. Lancet Neurol 11; 241-249.

30. Ketter N, Brashear HR, Bogert J, et al. Central review of amyloid-related imaging abnormalities in two phase III clinical trials of bapineuzumab in mild- to-moderate Alzheimer's disease patients. J Alzheimers Dis 2017; 57:557-573.

31. Miller C, Krasnow J, Schwartz LH. Medical Imaging in Clinical Trials. Springer.