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Amyloid-related imaging abnormalities (ARIA): diagnosis, management, and care in the setting of amyloid-modifying therapy

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Abstract

Amyloid-related imaging abnormalities, were originally described by dementia care experts. The wider use of aducanumab and now lecanemab warrant broader understanding by the health care provider continuum. The optimal care approach for patients with Alzheimer's dementia, treated with amyloid-targeted therapy, includes proper clinical diagnosis, complication surveillance, specific imaging protocols, expert specialty consultation, integrated treatment strategies, and proper facility system planning. Improved awareness and understanding of amyloid-modifying therapy, both benefits and potential complications, among the health care provider continuum is paramount to the success of complex care programs. Specifically, recognition of treatment high risk, high benefit groups, and the interface of concurrent antiplatelet and anticoagulation. This integrated acute, specialty, and primary care approach should improve patient care quality and outcome.

Introduction

Historically, the treatment of Alzheimer's disease has focused on behavior-modifying therapy as the only treatment option. The focus has shifted to agents of multiple mechanisms that modify disease course to varying degrees.

The advent of the significant use of novel anti-amyloid therapeutic interventions with clearly established benefits have allowed focus on broader aspects of care. This includes focus on amyloid-related imaging abnormalities (ARIA), that are found most commonly in those patients with Alzheimer's disease, who are being treated with amyloid-targeted monoclonal antibody treatments.

Early treatment trials identified characteristic cerebral MRI imaging findings designated as ARIA-E described as edema or sulcal effusions, and bleeding designated ARIA-H manifested as hemosiderin deposits or small parenchymal hemorrhages.

Interestingly, the presentations were often asymptomatic isolated imaging findings, or were found in the presence of untreated Alzheimer's disease as well.

Early research

There has always been an understanding since the early amyloid-B (AB)-lowering trials that is a variable incidence of asymptomatic ARIA.

Published in 2009, an early Phase II escalation trial with bapineuzumab enrolled 234 mild to moderate Alzheimer's disease patients who reported reversible vasogenic edema 9.7% (12) of patients with equal groups asymptomatic-50% (6) and experiencing transient symptoms-50% (6).[1] As well, there was a correlation to higher administered doses and APOE4 carrier status. This trend persisted in the 2014 Phase III trial publication, where 2452 total patients were enrolled, but eliminating the highest dose-2.0 mg/kg administered.[2]

In the 2018 release of Phase III results, when solanezumab was administered to 2129 total patients, where one treatment and two placebo patients were affected by asymptomatic edema and effusions.[3]

Recent evidence

The 2022 publication of the two aducanumab Phase III randomized clinical trials (RCTs)-EMERGE and ENGAGE described successful treatment of 3285 early Alzheimer disease patients.[4] Focused analysis of safety data, found the most common adverse event in the 10 mg/kg treatment group was ARIA-E occurring in 35.2% (362/1029) on at least one posttreatment cerebral MRI study. This phenomena was seen more commonly in APOE4 allele carriers. The symptomatic group- 9.1% (94/129) was most commonly afflicted with headache.

More focused analysis on adverse event profile finds that during the placebo-controlled period ARIA was found in 41.3% (425/1029); however this event was judged to be serious in only 1.4% (14) of patients. They noted that ARIA-E was the most commonly encountered-35.2% (362) adverse events, with the majority-72.7% (263) occurring early in the treatment course (<8 treatments).

Analysis of this adverse event profile finds that 26% (92) of this cohort were symptomatic. Those diagnosed with ARIA-E or ARIA-H (103) had headache-46.6% (48) as the predominant complaint, followed by confusion-14.6% (15), dizziness-10.7% (11), and nausea-7.8% (8). The vast majority of ARIA-E events-98.2% (479/488) resolved radiographically, with 82.8% (404/488) resolving within 16 weeks.

Interestingly, this finding was noted in the placebo group-2.7% (29/1076) with a 2.2% (16/742) incidence in APOE4 carriers, compared to 3.9% (13/334) in noncarriers. The presence of ARIA-H, specifically ARIA-microhemorrhage (mH) in 19.1% (197) and ARIA-superficial siderosis in 14.7% (151) of patients was found.

Late in 2022, the lecanemab study was reported, where 1795 patients were enrolled in a randomized Phase III trial for mild Alzheimer dementia patients.[5] Here, they noted infusion-related reactions in one quarter-26.4% of the participants, and amyloid-related imaging abnormalities with edema or effusions in 12.6%.

Likewise, data from the lecanemab double blinded Phase II trial and open label extension (OLE) demonstrated a low ARIA-E incidence of 10% with 3% that were symptomatic.[6] As with other studies, ARIA correlated with maximum drug serum concentration and APOE4 homozygous allele carriers. Clinical course involved largely asymptomatic presentations of mild to moderate disease that occurred early in the disease course (<3 months).

In 2023, the TRAILBLAZER-ALZ2 randomized clinical trial (RCT) was published describing the use of donanemab in those patients with early symptomatic Alzheimer's disease.[7] This international trial was a double blinded, placebo-controlled study that enrolled 1736 participants with 860 in the treatment and 876 in the placebo group. This early symptomatic group included those with mild cognitive impairment or dementia, as well as evidence of amyloid and tau pathology on positron emission tomography (PET).

They noted that ARIA-E edema or effusion lesions occurred in 24.0% (205), in the donanemab group, with 25% (52) of those symptomatic; compared to 2.1% (18) in the placebo group, with 0% (0) of those patients found to be symptomatic. The incidence of MRI determined ARIA-H was higher in the donanemab-31.4% (268) than placebo-13.6% (119) groups. As well, the mortality was 1.9% in the donanemab group compared to 1.1% in the placebo group associated with ARIA.

As well in 2023, the use of solanezumab in 1169 patients with preclinical AD was studied in a Phase III placebo controlled trial.[8] Here, ARIA-E with edema occurred at a 1% incidence in both treatment and placebo groups, while ARIA-H with hemosiderosis or microhemorrhages occurred in 29.2% in treatment and 32.8% in placebo group.

The majority of those with ARIA imaging abnormalities were largely asymptomatic, those with more severe symptoms ultimately had resolution of imaging abnormalities over time. However, significant ARIA abnormal were present in those with significant adverse outcome.

Pathophysiology

Early explanations of this phenomenon suggested a "leaky" blood–brain barrier.

This was related to amyloid deposits integrated into the vascular wall, and then their subsequent removal. These lesions associated with amyloid lowering therapy were initially described as vasogenic edema (VE) and microhemorrhages (mH).[9] These lesions were initially thought to be a continuum, but may be concurrent as they are recognized using different MRI sequences.

Therefore, vasogenic edema is typically extracellular outward leakage resulting from a disrupted blood–brain barrier accompanied by protein leakage, which is often reversible. This contrasts with cytotoxic edema, accompanied by sodium shifts where fluid accumulates in the intracellular space, requiring a different treatment strategy.[10]

Imaging

The diagnosis of ARIA requires MRI utilizing specific imaging protocol based on anticipated pathology—either edema (ARIA-E) or hemorrhage (ARIA-H), whether superficial siderosis or microhemorrhages.

Simplistically, T1 imaging has a more anatomical focus enhancing the fat based signal, while minimizing the water signal, often focusing on demyelination (Fig. 1A).[11] While T2 sequencing provides a more functional focus, enhancing the water based signal, focused on edema or ischemia (Fig. 1B). These protocols are optimized to include T2-weighted imaging, with fluid-attenuated inversion recovery (FLAIR) sequencing for edema (Fig. 2A).

The use of diffusion-weighted imaging (DWI) exhibiting a bright image associated with restricted diffusion in cases of cell swelling found earlier in the ischemic process compared to T1/T2 MRI (Fig. 2B).[12] The addition of

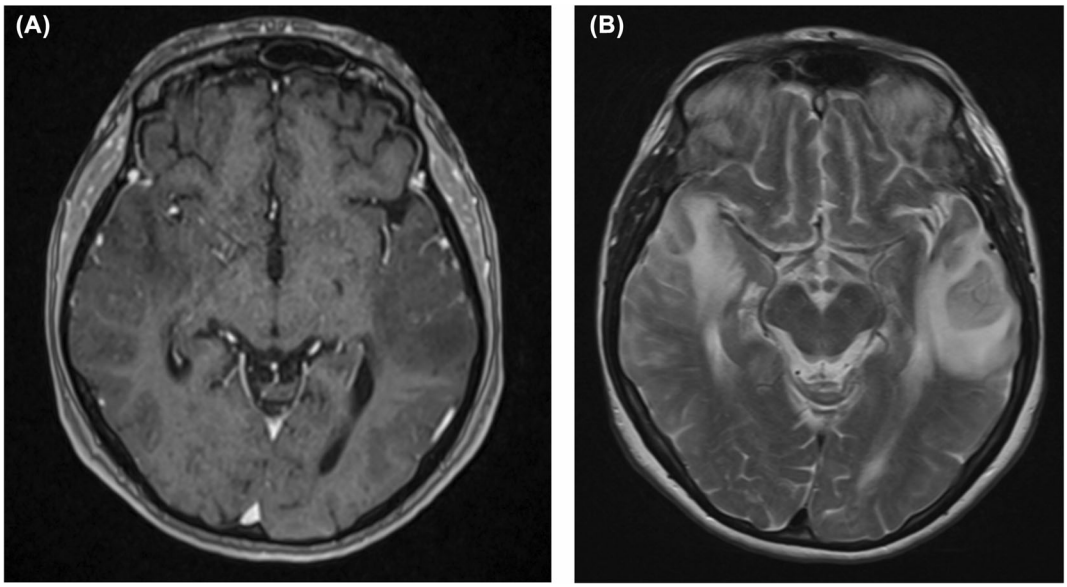

Figure 1. (A) ARIA MRI T1 axial (B) ARIA MRI T2 axial.

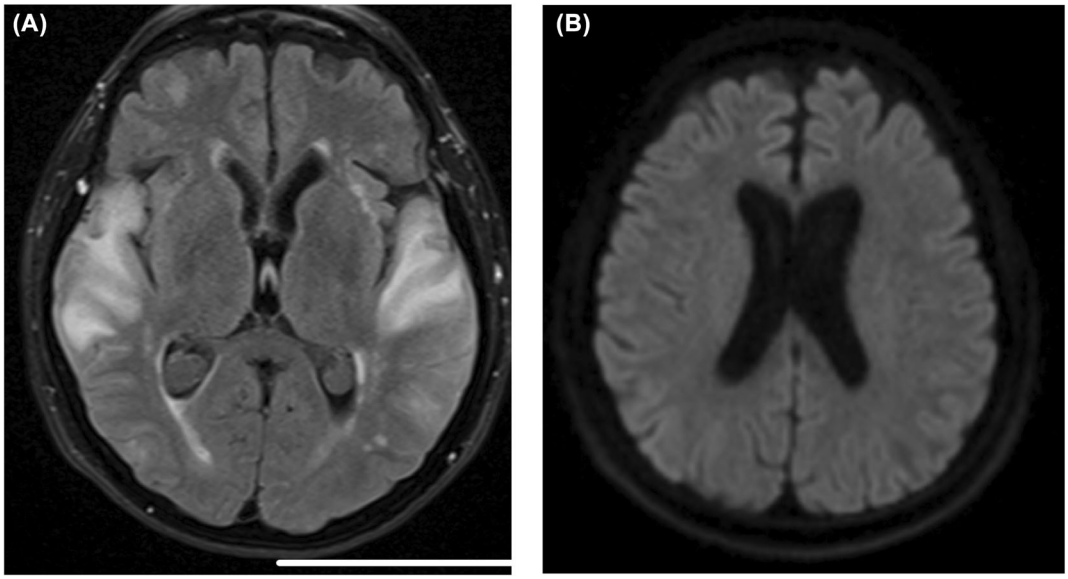

Figure 2. (A) ARIA MRI FLAIR axial (B) ARIA MRI DWI axial.

apparent diffusion coefficient (ADC) mapping calculated from the primary source image is reduced or dark in the restricted flow region typically representing cytotoxic edema, characterized by cell leakage, typically associated with cerebral ischemia (Fig. 3A).[13] However, the diagnosis of vasogenic edema, classically associated with cellular swelling from an inflammatory process tumor, infection or in this case ARIA can be facilitated by ADC formatting with pathology appearing hyperintense or bright, removing the T2 effect for clarity.

While microhemorrhages utilize T2 weighting emphasized by the addition of gradient refocused echo (GRE) and susceptibility-weighted imaging (SWI) to refine the diagnosis (Figs. 3B and 4).[14,15]

ARIA-E

This phenomenon was originally described as vasogenic edema, and was associated with altered permeability resulting in reversible extracellular edema, without cellular

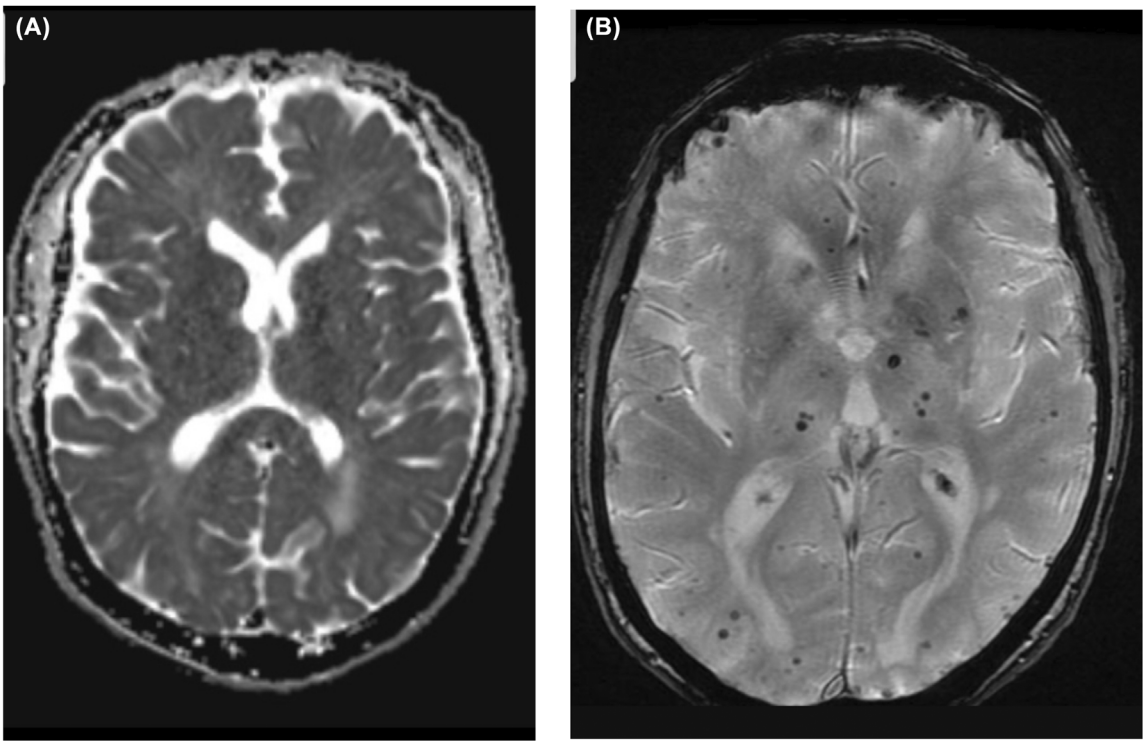

Figure 3. (A) CAA MRI ADC axial (B) CAA MRI GRE axial.

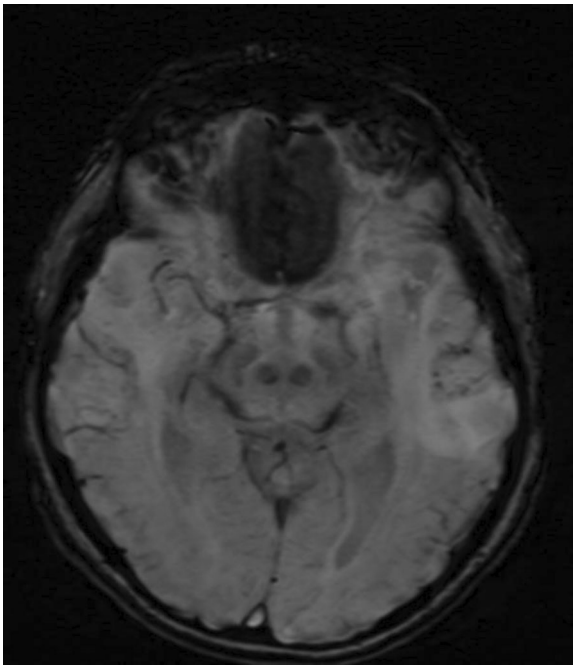

Figure 4. ARIA MRI SWI axial.

necrosis most consistent with cytotoxic intracellular edema best visualized on FLAIR MRI sequencing. This imaging technique suppresses background fluid such as cerebrospinal (CSF) fluid to accentuate superficial sulcal or periventricular brain lesions, such as those affected by multiple sclerosis or leptomeningitis.[16]

The term ARIA-E was utilized to describe MRI abnormalities in addition to parenchymal edema associated with effusion, or extravasated fluid in the sulcal space.[9] As well, the parenchymal edema is best visualized as T2 hyperintensities noted on FLAIR imaging denoting a reversible vascular leak without diffusion restriction localized to cortical or subcortical areas.[16]

ICH

Historically in the acute care setting, such as the ER or ICU, it was felt that non-contrast head CT was diagnostic test of choice for acute intracerebral hemorrhage.

In 2004, a prospective study of 200 patients examined with concurrent CT and GRE MRI found that MRI revealed any hemorrhage in 35.5% (71), while CT was positive in 14.5 (29%) patients ($p < 0.001$).[17] There was a 96% concordance in acute hemorrhage with hemorrhage diagnosed with both modalities in 14.5% (25) patients. MRI exclusively found 2.0% (4) acute hemorrhages and 24.5% (49) chronic hemorrhages, manifested as microhemorrhage. While, CT identified only 1 patient exclusively with subarachnoid hemorrhage (Table 1).

Table 1. Prospective evaluation of CT and MRI for acute intracerebral hemorrhage.

Study Patients 200				
Finding	MRI (%)	Both	CT	Significance
Hemorrhage	35.5 (71)		14.5 (29)	$p < 0.001$
Acute hemorrhage		12.5 (25)		
Hemorrhagic transformation	2.0 (4)		0	
Chronic hemorrhage	0		1.5 (3)	
Subarachnoid hemorrhage	0		0.5 (1)	
Microhemorrhage	24.5 (49)		0	

Source: Ref. [17].

They concluded that in the setting of stroke symptomology with focality, MRI may be as accurate as CT and is more accurate in the setting of chronic hemorrhage, most often manifested as microbleeds.

ARIA-H

Microhemorrhages, small parenchymal bleeds, or hemosiderosis, superficial surface iron deposits were then noted as potentially concurrent abnormalities with edema on T2-weighted gradient refocused echo (GRE) and post processing susceptibility weighted imaging (SWI) defining more subtle abnormalities.

GRE is adept at identifying hemosiderin deposits, likely related to previous micro bleeds that were not appreciated by computed tomography (CT) or other MRI protocols.[18] Interestingly, these lesions have a 9.8% incidence are commonly found in the lentiform nucleus, thalamus, and cortical–subcortical region related to systemic hypertension or previous cerebral hemorrhage.[19]

SWI is utilized to allow earlier detection of acute hemorrhage, usually within 6 h of onset exploiting the paramagnetic properties of deoxyhemoglobin.[20] As well, there allows a focus on previous small microbleeds and the potential for tissue viability assessment.

Risk factors

Cerebral amyloid angiopathy

There are a number of situations where ARIA appears to be more likely. The presence of relapsing inflammatory cerebral amyloid angiopathy (CAA-ri) is often associated with cortical superficial siderosis.[21] There largest longitudinal cohort finds that 37.1% were APOEe4 carriers, 36.3% had a history of Alzheimer's disease and 33.6% had a history of intracranial hemorrhage (ICH). In fact, those a previous history of ICH (52.6 vs. 14.3%, $p < 0.0001$) and occurrence of new ICH (19.3 vs. 3.6%, $p < 0.009$) more commonly presented with superficial siderosis. Therefore, CAA should be considered in the differential for patients presenting with ARIA-like findings, including those with history of ICH, Alzheimer's disease and those separately undergoing amyloid immunotherapy.

APOEe4

In a prospective case control two stage evaluation, during both the discovery phase of 319 patients there is an association between APOE e4 and lobar intracranial hemorrhage (ICH) (OR 2.09, $p < 0.001$), and the replication stage confirming the e4 association ($p = 0.004$) in 63 lobar ICH patients.[22] However, there was not an association with non-lobar hemorrhage in either group.

Likewise, there was not strong evidence of potentiation in subjects exposed to both warfarin treatment for atrial fibrillation and high risk APOE e variants. However, this observation may be limited by low prevalence of warfarin use.

Report of final MRI review by independent neuroradiologists in those with mild to moderate Alzheimer's disease treated in two Phase III trials with bapineuzumab involving 1331 apolipoprotein E gene-APOE e4 noncarriers and 1121 carriers identified 242 treatment-emergent ARIA-E patients in the final read process.[23] The overall incidence of ARIA-E was higher in APOE-4 carriers (active 21.2%, placebo 1.1%) than noncarriers (pooled active 11.3%, placebo 0.6%) and more often in homozygotes than heterozygotes (34.5% vs. 16.9%).

Preliminary data available from APOLLOE4, a Phase III trial of an investigational oral amyloid oligomer inhibitor-ALZ-801 (Alzheon) investigated those early stage AD patients, homozygous for the apolipoprotein e4 allele (APOE4/4).[24] This group at baseline demonstrated a higher prevelance of cerebral amyloid angiopathy (CAA) lesions, presumptively associated with ARIA-related edema and microhemorrhages (MH). Bleeding most commonly localized to frontal and occipital regions was manifested as lobar MH in 32%, ranging from 9% with superficial siderosis to multiple >4 MH in 9% of a 325 patient cohort with 2 patients exhibiting macrohemorrhage.[24,25] This finding is consistent with a class effect found in other amyloid-modifying therapy.

Amyloid lowering therapy dose

As well, there appears to be an established correlation between higher doses of anti-amyloid therapy and the presence of ARIA, including bapineuzumab, aducanumab and lecanemab.[1,2,4,5] The bapineuzumab trial series found a higher incidence of ARIA-E in noncarriers, as well as highest in earlier (Doses 1 and 2) compared to later treatment dosing.[26]

Anti-amyloid treatment protocols

The first widely adopted treatment protocol involving human immunoglobulin gamma 1 (IgG1) monoclonal antibodies utilized aducanumab that targeted both aggregated soluble and insoluble amyloid beta.[19,27] Examination of aducanumab trials EMERGE and ENGAGE, double blinded, randomized controlled studies explored both low-dose (3 or 6 mg/kg) and high-dose (6 or 10 mg/kg) infusion protocols every 4 weeks for 76 weeks.[4,28]

Inclusion criteria included enrolling those 50–85 years of age, confirmed amyloid pathology and clinical symptomology in those with Alzheimer's disease spanning the mild cognitive impairment to dementia continuum.[27,29] Here, it was crucial to note the study major exclusion criteria were specifically age > 85 years of age, previous transient ischemic attack (TIA) or stroke within the last year of screening, contraindication to cerebral MRI or PET imaging and use of antiplatelet or anticoagulant medication.

However in late January 2024, Biogen released in a corporate communication stating that they would reprioritize developmental resources allocated from aducanumab-avwa to lecanemab-irmb.[30] They will conclude the ENVISION Study, the Phase IV post marketing evaluation, but will continue to advance the science and care in this area.

Lecanemab as well targets both aggregated soluble and insoluble amyloid beta.[29] Clarity AD was the confirmatory Phase III, double blinded, randomized, placebo controlled trial where patients with mild MCI or AD who were 50–90 years of age with evidence of cerebral amyloid as defined by PET or CSF findings.[5] Impairment was defined as 1 standard deviation below age-adjusted mean of Weschler Memory Scale (WMS) IV-Logical Memory II assessment tool. They were administered intravenous lecanemab 10 mg/kg or placebo every 2 weeks with primary endpoint assessed at 18 months utilizing the Clinical Dementia Rating-sum of boxes (CDR-SB) assessment tool.

Lecanemab was initially approved in January 2023 under the US Food and Drug Administration (FDA)-accelerated approval pathway, which was then converted to traditional approval based on the clear clinical benefit demonstrated in the confirmatory trial.[31] However, they did note an increase in intracerebral hemorrhage in those that were on anticoagulants and treated with lecanemab.

Appropriate use recommendations for lecanemab administered early for mild cognitive impairment (MCI), or mild dementia due to AD with confirmation of brain amyloid pathology define the treatment and safety profile.[32] However, they noted the association of rare macrohemorrhage and severe microhemorrhages with anticoagulation. They recommended withholding treatment in those requiring mandatory anticoagulation.

Donanemab, as well is a monoclonal antibody experimental treatment protocol targeting AB Amyloid plaques defined in TRAILBLAZER-ALZ 2. It was compared to placebo was administered to patients 60–85 years with early symptomatic AD, administering 700 mg for 3 doses followed by 1400 mg intravenously every 4 weeks for up to 76 weeks.[7]

Overall, the group benefit effect of amyloid targeting therapies, including aducanumab, donanemab, lecanemab, and solanezumab, has been described in amyloid positive early symptomatic AD patients.[33] There was improvement noted in consolidated treatment group analysis comparing APOE e4 carriers, noncarriers and placebo, with slightly greater efficacy in carriers demonstrated.

However, the risk and severity of ARIA tends to be higher in carriers as well, warranting additional patient information concerning bleeding risk.

Adverse reaction

As we have discussed, adverse reactions, such as cerebral macrohemorrhage, microhemorrhage, or edema in the setting of concurrent anti-amyloid therapy are related to defined risk factors.[4,6,17–19]

First, a genetic predisposition defined as the presence of APOE-e4, incrementally based on heterozygous differing or homozygous identical alleles. Second, underlying cerebral pathology, such as cerebral amyloid angiopathy (CAA-ri) increases the risk of concurrent hemorrhage. Third, the use of anti-amyloid antibody therapy has a dose-related predisposition to adverse reactions. Fourth, the use of therapeutic antithrombotic medications, including antiplatelet and anticoagulant agents may pose additional bleeding risk.

Also present, are less significant infusion reactions associated with nausea, vomiting, arthralgia, and skin rash across the class.[1–8]

Clinical presentation

Earlier it was recognized by Sperling et al. that in the treatment setting ARIA-E most commonly presents in an asymptomatic fashion on routine radiological safety protocol MRI, but a small number of patients in the Phase I bapineuzumab had associated clinical mental status changes at some point in their treatment course.[9]

Based on the EMERGE and ENGAGE Phase III data summarized by Salloway et al. of the 1029 participants, receiving the high dose (10 mg/kg) aducanumab dose had an ARIA incidence of 35.2% (362), with ARIA-E subsequently occurring in 35.2% (362) of patients.[4] Here, 19.1% (197) of this cohort were felt to have exhibited treatment symptoms at some point in their course, which included headache, confusion, dizziness, and nausea (Table 2).

Table 2. Incidence of ARIA with amyloid-modifying therapy in early Alzheimer's dementia ARIA: ARIA-E and ARIA-H.

	Target (AB)	Dose (mg/kg)	Enrollment (*n*)	Placebo (%)	Treatment (%)
Agent				ARIA-E Carrier APOEe4	ARIA-E
Bapineuzumab	Monomer. Oligomer.	0.5, 1.0, 2.0 mg/kg	2452	0.2 (1) Noncarrier 0.2 (1)	15.3 (100) 4.2 (14)
Solanezumab EXPEDITION III	Monomer.	400 mg	2129	2.8 (30)	3.5 (62)
Gantenerumab GRADUATE I GRADUATE II	Fibril.	1020 mg	 985 980	Total Symptomatic	24.9 5.0
Aducanumab EMERGE. ENGAGE	Oligomer	10 mg/kg	1029	2.7	35
Donanemab TRAILBLAZER-ALZ2	Deposited	700–1400 mg.	1736	2.1 (18).	24.0 (52)
Lecanemab CLARITY AD.	Protofibril	10 mg/kg	1795	ARIA-E 1.7 (15). ARIA-H 7.4 (66)	 12.6 (113) 26.4 (237)

Source: Refs. [1–4,7,35].

Similarly, both headache and encephalopathy were reported in the setting of malignant hypertension and epileptiform activity in a patient diagnosed with ARIA-E who received a 6 mg/kg aducanumab dose as part of the ENGAGE trial.[34] Symptoms resolved with the radiographic abnormalities ARIA-E resolving by 6 months and the ARIA-H changes persisting.

Review of the gantenerumab Phase III trials-GRADUATE I and II reporting a 24.9% ARIA-E incidence in the treatment group.[35] As with other trials, this radiographic finding was identified in routine study screening. They reported that 5.0% were found to be symptomatic. These symptoms were nonspecific similar to other trials-headache, dizziness and confusion.

Differential diagnosis

The differential diagnosis can be broad, but the focus will be on those who have or are receiving amyloid lowering monoclonal antibody therapy.

Intracranial hemorrhage is the most concerning pathology for those caring for patients in the acute care setting. Typically, non-contrast head ct will be performed initially examining for signs of intracranial hemorrhage. Certainly catastrophic subdural, epidural, or intracerebral hemorrhage are unlikely to be confused with microhemorrhage. However, the presence of subarachnoid hemorrhage (SAH) in a classic diffuse superficial distribution may require delineation as ARIA-E associated effusions may enhance slightly.[36]

Cerebrovascular events can result in reversible ischemia, or defined infarct. Defined infarcts are typically associated with diffusion restriction in the acute disease phase lasting hours to days. While it is not later in disease course, the subacute phase lasting days to weeks, and the chronic phase lasting months to years. The acute phase of cerebral infarction typically affected by diffusion restriction on MRI with DWI is in contrast to ARIA, where there is typically an absence of diffusion restriction.[11]

However, confusion can still exist where those with ARIA can be diagnosed with stroke in an acute event, or primary microangiopathy in a subacute presentation. In the setting of anti-amyloid therapy, an acute neurological change accompanied by MRI focused hyper intensity may be consistent with ARIA or inflammatory cerebral amyloid angiopathy.[37] The use of repetitive MRI with FLAIR sequencing may help to differentiate an ischemic and inflammatory event.

However, it is difficult to distinguish between ischemia and an inflammatory cerebral amyloid angiopathy based on imaging alone. Clearly, ARIA has a significant likelihood in the setting of amyloid monoclonal therapy, but remains a diagnosis of exclusion in the acute setting.

Infectious conditions such as encephalitis, typified by more diffuse parenchymal brain involvement; and meningitis, involving superficial inflammation localized to the subarachnoid space. The latter may potentially be confused with ARIA-E, specifically with effusion localized to the superficial cortical region. Abscess is often demonstrated as a rim enhancing lesion with central clearing on

contrasted MRI compared to ARIA with a more uniform appearance.

Another inflammatory condition to consider is the Posterior Reversible Encephalopathy Syndrome (PRES), a reversible condition associated with altered mental status, seizures or headache.[38] This condition often presents with posterior occipital or parietal localization, occurs in the setting of significant hypertension, features headache and visual changes often associated with renal disease or pregnancy. Typically, PRES is manifested as bilateral, symmetric, hyperintense posterior edematous lesions without hemorrhage compared to ARIA, which may have a more asymmetric, but also have a dependent distribution.

Lastly, cerebral malignancy whether primary or secondary, can be accompanied by vasogenic edema manifested as contrast enhancing MRI lesions, that may have central necrosis or clearing or sporadic hemorrhage.

Disease course

As with most conditions our primary goal is proper disease diagnosis, either inclusion or exclusion, hopefully followed by an estimate of disease severity. In setting of ARIA, the initial correlation described a MRI based radiographic grading system defining ARIA-E, ARIA-H microhemorrhage, and ARIA-siderosis rated mild, moderate, and severe classification (Table 3).[2,21,37–40]

As the presence of ARIA is clearly related to the administration of anti-amyloid therapy, the first question is impact on ongoing anti-amyloid disease treatment. There is a graded recommendation approach that allows anti-amyloid therapy to be continued, held and resumed, undergo dosage modification or finally discontinued all together (Table 4).

Treatment

Simplistically, the treatment strategy in the presence of ARIA in the setting of amyloid lowering therapy is a clinical severity and radiologic appearance based evaluation protocol.

Table 3. MRI-defined ARIA severity levels.

	Severity		
Condition ARIA	Mild	Moderate	Severe
ARIA-E			
Site number[a]	1	2	3
Size	<5 cm	5–10 cm	>10 cm
ARIA-H			
Microhemorrhage new	<4	5–9	>/−10
Superficial siderosis focal	1	2	>2

Source: Adapted from: Refs. [2,21,37,39,40].
[a]ARIA-E FLAIR hyperintensity location sulcus, cortical, subcortical tissue white matter.

Table 4. Occurrence of ARIA E/H and effect on anti-amyloid treatment modifications.

Pathology	MRI appearance		ARIA-E	ARIA-H
Symptom severity	Mild	Moderate	Severe	
Asymptomatic	Continue	Suspend	Suspend	Discontinue
Symptomatic	Suspend	Suspend	Suspend	Discontinue
Severe	Discontinue	Discontinue	Discontinue	Discontinue

Source: Adapted from Refs. [4–6].

First, incidental discovery of ARIA-E in the presence of asymptomatic patient would typically warrant continued therapy. Second, the presence of more moderate symptoms in both ARIA-E and ARIA-H patients would warrant suspension of dosing protocol. Finally, severe symptoms, especially in the setting of ARIA-H would warrant discontinuation of therapy.

The onset of this radiographic change was found early in therapy, during dose titration or just at the time strategic-targeted dose was reached, and not commonly during maintenance therapy.[4,23,37]

Supportive therapy

As with any significant intracranial insult, supportive therapy is key to recovery. The presence of posterior reversible encephalopathy syndrome (PRES), described as vasogenic edema localized in posterior–occipital and parietal regions, often associated with renal failure, pre-eclampsia, medication effect, or significant hypertension.[38] In PRES, treatment may include discontinuing the offending agent, and aggressive blood pressure control. Interestingly, with this etiology of vasogenic edema, treatment with corticosteroids do not appear to be effective in PRES.

Edema

Additional treatment strategies have been largely selective in implementation. The presence of brain edema accompanies diverse injury types and can impact outcome with a direct effect on intracranial pressure (ICP). Vasogenic edema occurs initiated by BBB disruption, with protein extravasation and extracellular fluid leakage. While, cytotoxic edema is denoted by cellular swelling associated with intracellular fluid entry, and best defined by the addition of DWI sequencing to standard MRI imaging.[10,39]

Cerebral amyloid angiopathy

There is clear evidence that inflammatory conditions, such as cerebral amyloid angiopathy can respond to

immunosuppressive agents, such as corticosteroids or cyclophosphamide.[20,21,40,41] The use of immunosuppressive agents may reduce the autoantibody response to amyloid beta that stabilizes small vessel integrity.[41]

There is evidence that CAA-ri is a reversible condition with good response to immunomodulatory drugs. The use of high-dose pulse steroids, administered early in disease course improves outcome in this population.[21] Regenhart's summary reported an analysis of 87 patients treated with five successive intravenous doses of 1 g/d methylprednisolone, followed by 1 mg/kg oral daily dosing with recurrence prevention.[42]

Treatment

This raises the question of the potential for a similar vascular stabilization effect in ARIA patients. Symptomatic ARIA-E is presumptively associated with excessive neuromodulation, so recommendations to evaluate high dose corticosteroids- methylprednisolone or dexamethasone, that penetrate the blood brain barrier (BBB) improving severity or duration of amyloid treatment-related adverse effects.[37] The empirically recommended strategy is a 3–5 day course of 1 g of intravenous methylprednisolone, followed by an oral prednisone taper over the next few weeks with seizure prophylaxis as necessary.[43,44] Similarly, the use of plasmapheresis has been utilized in severe ARIA-E cases as well.

Anticoagulation

As part of the Alzheimer's disease (AD) multifactorial etiologic theory, the significance of the hemostatic vascular component should be considered. One suggested approach is the early use of direct oral anticoagulants (DOACs) to counteract pro-inflammatory effects of amyloid, thrombin and fibrin induced change affecting cerebral vasculature. They postulated anticoagulants could inhibit the thrombin to fibrin conversion with subsequent vascular degeneration avoiding decreased microcirculatory flow, which may favorably effect subsequent neurodegeneration.[45]

However, this treatment strategy, or incidental anticoagulant use to prevent further vascular ischemia raises an additional concern. Although, no defined direct amyloid lowering therapy interaction, it is prudent to be cautious in those treated with anticoagulants. These should include conventional anticoagulants, such as warfarin or heparin.

Novel anticoagulants that include factor Xa inhibitors, such as rivaroxaban, apixiban and edoxaban and direct thrombin inhibitors, such as argatroban or dabigatran may be associated with a higher incidence of bleeding and should be monitored carefully if administered.

Clearly in the acute treatment setting with sudden onset neurological deficit, extreme caution is warranted with the prospect of systemic TPA administration. The published case correspondence referencing multiple cerebral hemorrhages in the setting of previous lecanemab therapy where TPA was administered for acute ischemic stroke has been noted.[46]

In addition, a fatal iatrogenic cerebral B amyloid-related arteritis associated with extensive microhemorrhages in the open label extension of the clinical trial in a homozygous APOE4 patient.[44]

This has been noted in the updated ARIA risk "black box" warning, for brain swelling and bleeding risk, including fatal brain hemorrhage.[47] However, it is important to recognize that hemorrhage can occur in normal dementia progression. As well, other neurologic treatment interventions such as thrombolysis with intravenous recombinant tissue plasminogen activator (r-TPA) administered to 2%–5% for those with acute ischemic stroke is associated with a symptomatic intracranial rate as high as 6%.[48]

A focused risk–benefit analysis for should be performed for patients taking antiplatelet or anticoagulant agents chronically noting the risk of severe bleeding. This specific focus on the use of thrombolytic agents in the setting of acute stroke symptomology would warrant primary consideration of alternative acute stroke interventions, such as mechanical thrombectomy in the setting of a new significant acute neurological deficit.

Care resources

As with any resource intensive clinical program, such as those providing transplant, bariatric surgery, or acute trauma, amyloid-modifying therapy programs warrant the same comprehensive analysis. These multidisciplinary programs require standardized diagnosis, treatment and stabilization procedures and protocols. This would ensure that proper patients are selected for treatment, balancing risks, benefits, and the right to self-determination.

Expert panel recommendations for the use of aducanumab establish the basis for patient diagnosis, enrollment and treatment.[39] Likewise, the use of established patient care registries, such as the ALZ-NET Treatment and Diagnosis Registry ensure continual care tracking, comparison, and improvement.[49]

However, the acute care plan focuses on potential treatment complications and requires active primary care, emergency medicine and critical care medicine understanding and input as well (Fig. 5). First, the ideal program will partner with an acute care facility with expertise in complex patient management. Second, the implementation of a multidisciplinary team approach, including physicians,

1. Complex Patient Management Expertise
2. Multidisciplinary Team Approach
3. Emergency and Critical Care Medicine Resources
4. Experienced Dementia Care Neurologist
5. Neuroradiology Capability
6. Provider Network and Patient Care Registry
7. Patient and Family Education

Figure 5. Amyloid-modifying therapy facility acute care program essentials. (1) Complex patient management expertise. (2) Multidisciplinary team approach. (3) Emergency and critical care medicine resources. (4) Experienced dementia care neurologist. (5) Neuroradiology capability. (6) Provider network and patient care registry. (7) Patient and family education.

nursing and paraprofessional staff is most successful for complex care scenarios. Third, the presence of acute care resources are essential, including both emergency medicine and critical care capability. Fourth, the presence of neurologist, experienced in dementia care is essential for a well-functioning program. Fifth, a definitive requirement is the presence of advanced radiology resources, including PET imaging and neuroradiology capability. Sixth, participating in a provider network or patient care registry helps to formalize the care process. Finally, providing patient and family education concerning diagnosis, treatment and facilitate understanding of disease course.

Conclusion

As with some other neurological conditions, the greater the preexisting pathology, the greater the potential benefit of some treatment, but as well the commensurate risk of potential adverse effects.

Patient risk stratification is improved by focusing on genetic risk profile-APOE4/4 homozygosity, cerebral amyloid burden, necessity of anticoagulation use, and disease progression.

There is now clear concern over the concurrent use amyloid lowering therapy combined with acute thrombolytic, antiplatelet, or anticoagulant therapy that may warrant therapy discontinuation.

The Alzheimer's disease and related dementia journey for patients and family is intimate and personal with evidence based treatment decisions individualized to the specific patient care event with physician guidance.

With the advent of more widespread amyloid-modifying treatments, health care systems will benefit by a structured patient care evaluation and treatment program emphasizing acute emergency care strategies as well.

Author Contributions

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Conflict of Interest

The authors have no conflict of interest to declare.

Data Availability Statement

Public access imaging.

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