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Insights on amyloid-related imaging abnormalities from the "Pre-Alzheimer's disease Alliance of China"

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Abstract

Alzheimer's disease (AD) is the most common cause of dementia and accounts for 60 – 80% of all such cases. For approximately 20 years, the research and development of new drugs for AD all ended in failure; however, aducanumab was recently granted accelerated approval by the US Food and Drug Administration. Aducanumab is a representative passive anti-β-amyloid (Aβ) immunotherapy and is the only approved drug that directly targets the pathological changes of AD; it can significantly reduce brain Aβ deposition, which is a hallmark of AD. During the clinical trials of amyloid-targeting monoclonal antibodies, represented by aducanumab, amyloid-related imaging abnormalities (ARIA) were the most common and important adverse reactions. Therefore, before the large-scale clinical application of amyloid-targeting monoclonal antibodies, clinicians and radiologists need to fully understand ARIA so that they can make more informed decisions. Considering the very uneven distribution of medical resources in China, we — on behalf of the "Pre-AD Alliance of China" — believe that it is necessary to write a consensus to elaborate on the mechanisms, risk factors, identification methods, and administration processes of ARIA.

Keywords: Alzheimer's disease; Amyloid-related imaging abnormalities; Edema; Sulcal effusion; Microhemorrhage; Superficial siderosis

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1. Introduction

According to the latest research report of the World Health Organization (https://www.who.int/health-topics/dementia#tab=tab_1), it is estimated that more than 55 million people live with dementia worldwide. Notably, dementia is currently the seventh leading cause of death among all diseases, and is one of the major causes of disability and dependency among older adults. Among all types of dementia, Alzheimer's disease (AD) is the most common and accounts for 60 – 80% of all cases[1]. Although the incidence of AD has demonstrated a declining trend in some affluent countries, the situation remains less optimistic in developing countries[2-4]. In China, the number of AD-affected patients exceeds 9 million[5], and the socioeconomic losses caused by AD

alone reached US $248.71 billion in 2020[6,7], placing a large burden on the country, society, and families. Consequently, effective anti-AD drugs are urgently needed to prevent the progression of this disease.

AD is a complex and progressive disease characterized by the extracellular deposition of anti-β-amyloid (Aβ), in the form of neuritic plaques, and intraneuronal neurofibrillary tangles, which are composed of aggregated hyperphosphorylated tau proteins[8]. The journey of drug development for AD has not been a smooth one. Only six drugs had been approved by the US Food and Drug Administration (FDA) before 2021, and each one only improves AD symptoms[9,10]. Based on the "amyloid cascade hypothesis" and real-world studies, Aβ is regarded as the earliest abnormal change in AD. This is followed by the aggregation of cortical tau tangles, ultimately resulting in neurodegeneration and cognitive decline[8,11-14]. Furthermore, the latest research framework of the National Institute on Aging–Alzheimer's Association states that individuals with evidence of abnormal Aβ biomarkers are on the Alzheimer's continuum[15], indicating an increased risk of cognitive decline compared with individuals with normal levels of Aβ biomarkers[16]. It is, therefore, not surprising that most anti-AD drugs target amyloid[17]. The FDA recently conditionally approved aducanumab as an anti-amyloid drug for AD treatment, which comes approximately 17 years after the approval of memantine in 2003. Aducanumab is a typical representative passive anti-Aβ immunotherapy and is currently the only drug that directly targets the clearance of Aβ pathology in AD[18]. The approval of aducanumab paves the way for the further development of amyloid-targeting monoclonal antibodies and offers hope to patients with AD.

In addition to effectiveness, safety is an important evaluation index for the approval of new drugs. Amyloid-related imaging abnormalities (ARIA) are the most important adverse effect of amyloid-targeting therapies. This term refers specifically to abnormal imaging manifestations (rather than clinical manifestations). ARIA was first reported in a clinical trial of bapineuzumab in 2009[19]; subsequently, it has been found to be generally related to other monoclonal antibodies, including aducanumab[20]. An "ARIA paradox" has been proposed, which assumes that Aβ mobilization may be casually linked to both efficacy and ARIA risk[21]. The spectrum of ARIA includes vasogenic edema and/or sulcal effusion — this is termed ARIA-edema (ARIA-E), and its exudative components are mainly protein liquid components — as well as microhemorrhage and/or superficial siderosis — this is termed ARIA-hemorrhage (ARIA-H), and its exudative components are mainly hemosiderin[22,23]. Clinicians and radiologists need to fully understand ARIA before popularizing these amyloid-targeting monoclonal antibodies, such as aducanumab. Therefore, the main aims of this recommendation are to introduce the mechanisms, recognition, and management of ARIA in the hope that patients with AD will benefit in the near future.

2. Identification of ARIA

2.1. Clinical features

Most ARIA events have no clear accompanying symptoms and can only be detected by imaging. For example, the results of aducanumab Phase III studies indicated that approximately 74% of participants with ARIA were asymptomatic[24,25]. Furthermore, among those with symptomatic ARIA, symptoms were mild in 67.7%, moderate in 28.3%, and severe in just 4%. The most common symptoms reported were confusion or altered mental status (5%), dizziness (4%), visual disturbances (2%), and nausea (2%). Notably, the ARIA episodes generally resolved within 4 – 16 weeks, and the majority of patients who experienced ARIA were able to continue treatments; only 6.2% patients discontinued the trial. Similar results have been reported with other drugs, such as bapineuzumab; 78% of participants did not report ARIA-associated symptoms, and the adverse events reported in symptomatic patients mainly included headache, confusion, and neuropsychiatric and gastrointestinal symptoms[26]. In general, ARIA needs to be distinguished from pathologies such as stroke (ischemic or hemorrhagic), subarachnoid hemorrhage, reversible posterior encephalopathy syndrome, and cerebral amyloid angiopathy-related inflammation (CAA-ri). There are many similarities between ARIA and CAA-ri, and their differentiation mainly depends on each patient's medical history. Typical idiopathic CAA-ri usually occurs naturally; that is, it is not drug induced[21]. In addition, in CAA-ri, the number of microhemorrhages in the edema area of the brain parenchyma is usually higher than in ARIA.

2.2. Recognition sequences

Although some ARIA can be identified using computed tomography, magnetic resonance imaging (MRI) remains the main identification method[23]. MRI studies for ARIA should include T2-weighted/fluid-attenuated inversion recovery (FLAIR), T2* gradient refocused echo (GRE), and rapid diffusion-weighted imaging (DWI). Depending on the type of MRI available, an optional fourth sequence could be either three-dimensional (3D) T1 or 3D T2 sampling perfection with application-optimized contrasts using different flip angle evolutions (SPACE)[23,24]. In clinical trials of amyloid-targeting monoclonal antibodies, the

Alzheimer's Association Research Roundtable Workgroup suggested that researchers should use FLAIR sequences to recognize ARIA-E, and GRE or susceptibility-weighted imaging (SWI) sequences to recognize ARIA-H[22]. When an in-depth understanding of the lesions is required, radiologists must decide whether additional imaging sequences, such as with gadolinium enhancement, are needed[23].

In an ongoing, recent, real-world study of aducanumab (NCT05097131), researchers used 3D T2 FLAIR to identify ARIA-E events with a resolution ratio of 1.2 mm × 1.0 mm × 1.0 mm, 2D T2* GRE to identify ARIA-H events with axial positions and a resolution ratio of 1.0 mm × 1.0 mm × 5.0 mm, and additional DWI with a resolution ratio of 2.0 mm × 2.0 mm × 5.0 mm. The field strength was 1.5 or 3.0 T. Considering the severe imbalance in the distribution of medical resources in China, we believe that MRI sequences should not be strictly defined, but that both ARIA-E and ARIA-H need to be considered. The specific details should be jointly decided by both radiologists and clinicians after consideration of the situation. We make the following suggestions: (1) use FLAIR to identify ARIA-E, (2) use T2* GRE or SWI to identify ARIA-H, (3) use DWI to evaluate the degree and types of edemas, and (4) use conventional T1 sequences to display anatomical structures and make any comparisons that may be required with the enhanced sequences. We suggest a field strength of 3.0 T with slice thickness ≤5.0 mm and echo time ≥20 ms.

2.3. Imaging features

The vasogenic edema of ARIA-E usually manifests as increased MRI signal in multiple regions of the hemisphere in FLAIR images, affecting both gray and white matter (Figure 1A and 1B), and the sulcal effusion usually demonstrates increased MRI signal in sulci (Figure 1C and 1D), which represents proteinaceous fluid tracking in the leptomeninges and sulcal spaces[22,23,26]. Both subtypes are transient in nature, are not associated with reduced diffusion abnormalities, and can be distinguished by differences in anatomical sites[23]. ARIA-H (microhemorrhage) typically manifests as a focal, round, very low-intensity (relative to the adjacent brain) lesion in the brain parenchyma. It can be detected on appropriate MRI sequences, and the lesion diameter is usually <10 mm (Figure 1E)[22,23,26]. In contrast, superficial siderosis refers to curvilinear low intensities adjacent to the surface of the brain (Figure 1F); it is caused by iron depositions in the form of hemosiderin, and indicates that blood is leaking from vessels to the adjacent subarachnoid or perivascular space[22,23,26]. Notably, the conspicuity of microhemorrhage and superficial siderosis can be enhanced or diminished by specific image acquisition attributes; for example, ARIA-H is almost invisible on T1, T2, and FLAIR sequences[23]. For patients who have received treatment, all newly discovered lesions must be fully analyzed to exclude other possible pathological changes, especially lesions on FLAIR images.

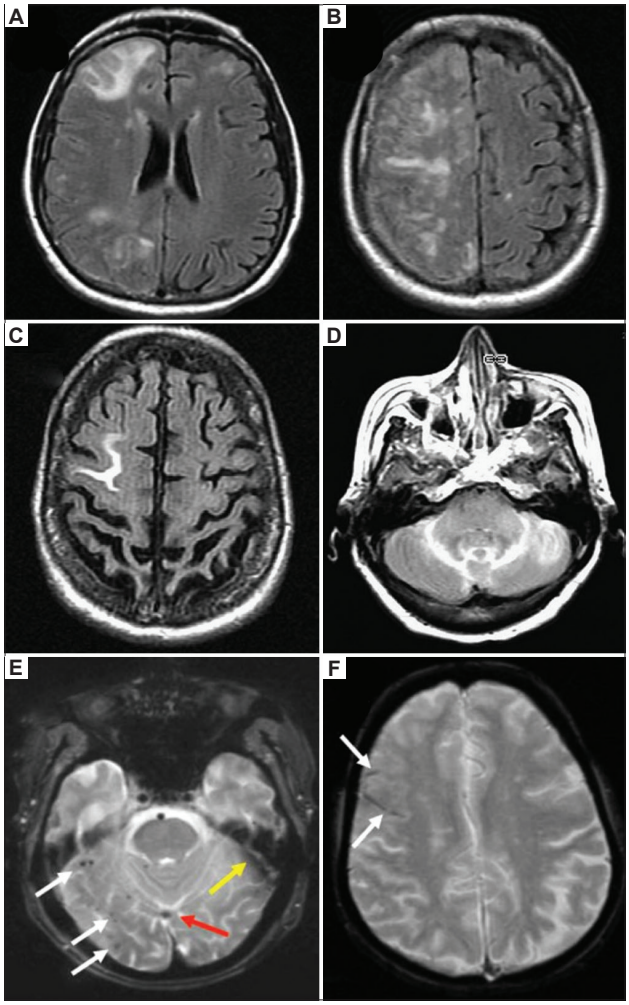

Figure 1. Typical images of amyloid-related imaging abnormalities (ARIA). (A, B) ARIA-edema (ARIA-E) (vasogenic edema) as seen on fluid-attenuated inversion recovery (FLAIR) images, demonstrating increased signal in multiple regions of the right hemisphere, affecting both gray and white matter. (C, D) ARIA-E (sulcal effusion) detected on FLAIR images, demonstrating increased signal in sulci, which is thought to represent proteinaceous fluid tracking in the leptomeninges and sulcal spaces. (E) The white arrows indicate multiple dark foci in the right inferior temporal and occipital lobes, suggesting ARIA-hemorrhage (ARIA-H) (microhemorrhage); the red arrow indicates the inferior sagittal sinus, and the yellow arrow indicates a susceptibility artifact because vascular structures and artifacts can sometimes mimic the appearance of microhemorrhage and siderosis. (F) The white arrows indicate curvilinear dark sulci in the right frontal lobe, which is typical of the appearance of ARIA-H (superficial siderosis). Both (E) and (F) were acquired as gradient refocused echo sequences. All images are copied and modified from "*Sperling, R.A., et al., Alzheimer's Dement, 2011, 7(4): p. 367-85.*"; the copyright belongs to the original authors and/or the publisher.

A diagnosis of ARIA depends on both clinical and imaging findings. It is generally easy for researchers to identify ARIA using the standardized protocols of clinical trials such as those of aducanumab[24]; the rigorous monitoring of MRI and new-onset symptoms during the titration period largely ensure the early recognition of ARIA. However, it should be noted that some individuals have spontaneous vasogenic edema at baseline, although the proportion is very low (typically <0.1%)[27]. Furthermore, as age increases, the probability of spontaneous superficial siderosis and microhemorrhage also increases; specifically, the incidence rate of spontaneous superficial siderosis increases from 0.21% at 50 to 69 years old to 1.43% at >69 years old[28], and the rate of spontaneous microhemorrhage increases from 18% at 60 to 69 years old to 38% at >80 years old[29]. These spontaneous events need to be differentiated from drug-induced events. In addition, radiologists should be trained to ensure diagnostic reliability. In a retrospective study, compared with judgment by professional radiologists, 84% of cases were missed at an initial audit by local radiologists, whereas only 14% were missed after training[30].

3. Risk factors for ARIA

We should first clarify whether all amyloid-targeting monoclonal antibodies can lead to ARIA. Integrated data from aducanumab Phase III studies (EMERGE and ENGAGE) suggest that ARIA (both ARIA-E and ARIA-H) occurred in 35.2% of patients taking high-dose aducanumab compared with 2.7% of the placebo group, indicating that aducanumab is associated with a substantially increased rate of ARIA compared with that observed in natural history studies or trial placebo groups[24]. In addition, an important meta-analysis recently suggested that amyloid-targeting therapy indeed increases the risk of ARIA by a large effect size, with a relative risk of 4.30 (95% confidence interval: 2.39 – 7.77). Further subgroup analysis revealed that all drugs were responsible for this increase except for solanezumab, whose low ARIA risk may be attributed to its preferential targeting of monomeric Aβ (rather than Aβ species deposited in plaques)[31].

The present evidence suggests that the clearest and most important factors for ARIA occurrence are a high therapeutic dose and being a carrier of apolipoprotein E (APOE) ε4 allele. In a retrospective analysis of three bapineuzumab Phase II studies, researchers found that ARIA-E incidence increased with bapineuzumab dose (hazard ratio: 2.24/mg/kg increase in dose) and with *APOE ε4* allele number (hazard ratio: 2.55/allele) using Cox proportional hazards models[26]. In bapineuzumab Phase III studies, the incidence proportions of treatment-emergent ARIA-E in *APOE ε4* non-carriers were 5.6%, 13.4%, and 19.9% for the 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg groups, respectively, compared with 0.6% in the placebo group[32,33]. In the EMERGE study of aducanumab, the incidence rates of ARIA-E in the low-dose and high-dose groups were 25.7% and 34.0%, respectively; very similar results were reported in the ENGAGE study, with rates of 25.4% and 35.5%, respectively[25]. Researchers have also observed a dose-dependent effect of gantenerumab; the incidence rates of ARIA-E were 0.8%, 6.6%, and 13.65% in the placebo, 105 mg, and 225 mg groups, respectively[34]. Similar results have been reported for other monoclonal antibodies, such as lecanemab[35]. In contrast, the incidence rate of ARIA-H does not significantly increase with a higher therapeutic dose. In one study, participants without the *APOE ε4* allele had an incidence rate of ARIA-H of 12.3% for the 105 mg gantenerumab group and 11.0% for the 225 mg gantenerumab group; among subjects with one *APOE ε4* allele, the rates were 19.8% and 19.4%, respectively[34]. In aducanumab Phase III studies, although ARIA-H (superficial siderosis) showed a dose-dependent effect in the high- and low-dose groups (13.3% vs. 9.2% in EMERGE, 15.4% vs. 8.8% in ENGAGE), there was no clear difference in the incidence rate of ARIA-H (microhemorrhage) between the two groups (18.6% vs. 16.2% in EMERGE, 17.6% vs. 15.5% in ENGAGE)[25]. In addition, mounting evidence has confirmed that carrying the *APOE ε4* allele also significantly increases ARIA-E incidence. For example, compared with an occurrence rate of 20.3% in *APOE ε4* noncarriers, 43% of patients with the *APOE ε4* allele developed ARIA-E with high-dose aducanumab treatment[24]. Furthermore, among participants receiving lecanemab, ARIA-E was observed most commonly in participants who were *APOE ε4* carriers, and least often in those who were noncarriers (14.3% vs. 8.0% in the 10 mg/kg biweekly group; 10.2% vs. 7.1% in the 10 mg/kg monthly group)[35]. Comparatively few studies have analyzed the correlation between ARIA-H and *APOE ε4* status, but there is evidence that ARIA-H incidence is also likely to occur in an *APOE ε4* genotype-dependent manner[34-36]. For example, *APOE ε4* allele frequency, the pre-existence of small microhemorrhages, treatment with bapineuzumab, and the use of antithrombotic agents are all associated with an increased risk of ARIA-H[36]. Furthermore, integrated data from aducanumab studies have suggested that ARIA-E and ARIA-H are highly correlated. Specifically, ARIA-H microhemorrhage and superficial siderosis were both more common in participants with ARIA-E (40.3% and 38.7%, respectively) than in participants without ARIA-E (7.6% and 1.6%, respectively); moreover, among participants with both ARIA-E and ARIA-H, these two events frequently overlapped temporally[37].

Vascular risk factors such as hypertension, hyperlipidemia, and diabetes do not seem to be risk factors for ARIA-E[33]. Furthermore, baseline biomarkers of amyloid positron emission tomography imaging, volumetric MRI measures, and most cerebrospinal fluid biomarkers also have no associations with ARIA-E, although lower baseline cerebrospinal fluid levels of $A\beta_{42}$ in *APOE ε4* noncarriers has been associated with a higher risk of ARIA-E[38]. The correlation between baseline microhemorrhages and ARIA is also debatable; current studies have reported inconsistent results[26,32,36].

Despite the relatively high incidence rate of ARIA in subjects who used amyloid-targeting monoclonal antibodies compared with subjects who used placebo, there is no need to be pessimistic. Most ARIA is asymptomatic (see section **2.1**), and a dose titration strategy is likely to reduce the occurrence of ARIA to a certain extent[39]. In addition, standardized management protocols can also enable clinicians to make early decisions[24]. Moreover, the cumulative risk of ARIA decreases with multiple infusions of antibodies[25,26,32,36,40,41]. For example, in patients treated with bapineuzumab, the incidence rate of ARIA-H was elevated in the initial 6 months of active treatment only, and declined after this interval to a rate similar to that observed in the group treated with placebo[36]. Similar results were obtained with aducanumab[25].

4. Mechanisms of ARIA

While the mechanisms underlying ARIA are not completely understood, it is likely that the coexistence of multiple pathways leads to the occurrence of ARIA. Clinical trials have demonstrated a significant correlation between ARIA-E and ARIA-H[37], indicating that they may have a common pathophysiological mechanism.

The current mainstream view is that ARIA results from a large amount of Aβ being cleared in a short period of time[42]. More specifically, the solubilization of Aβ caused by amyloid-targeting monoclonal antibodies overwhelms the capacity for Aβ clearance through the perivascular pathways, leading to amyloid deposition in the arterial wall and accelerated the development of CAA. Furthermore, specific therapies also target vascular Aβ and thus disrupt vessel integrity, contributing to vascular leakage. As a result, patients show ARIA on neuroimaging when liquid components, proteins, or cellular components leak into the surrounding tissues. This viewpoint is also supported by the following line of evidence. First, *ApoE ε4* carriers have more severe Aβ deposition than *ApoE-ε4* non-carriers[43]; multiple studies have demonstrated a positive association between *APOE ε4* allele dose and ARIA incidence[32,36]. Second, the risk of ARIA increases with the dose of amyloid-targeting monoclonal antibodies, indicating that a higher level of Aβ clearance leads to a higher incidence of ARIA[26,32,39]. Third, with the continuous use of amyloid-targeting monoclonal antibodies and the continuous removal of Aβ, the structural integrity of vessel walls and the efficiency of perivascular drainage may improve, thereby gradually reducing the incidence of ARIA[26,42]. Similar results have been reported in animal models. Zago *et al.* found that the clearance of vascular Aβ was spatially and temporally associated with microhemorrhage when an AD mouse model was treated with amyloid-targeting antibodies; this microhemorrhage was transient and improved with the restoration of vascular morphology[41].

Capillary amyloid deposition and alterations of the blood–brain barrier are also likely to be involved in ARIA. The solubilization of parenchymal Aβ leads to its accumulation in capillaries, while capillary Aβ deposits can change the normal tight structures of astrocytic endfeet surrounding endothelial cells[41]. Similar results have been reported in the brains of participants who received immunotherapy; researchers found that astrocytic endfeet may be damaged with the progression of capillary amyloid-related angiopathy, thus causing uncontrolled fluid influx to the perineural space, leading to ARIA-E[44]. In another study, Blockx *et al.* directly observed disruptions of the blood–brain barrier using a series of repeated gadolinium-enhanced T1-weighted scans and a T1 mapping model. Notably, the disruption events were also transient and resolved quickly[45]. Aquaporin-4 is a bidirectional water channel that facilitates the reabsorption of excess fluid during conditions of brain edema. In animal models, capillary Aβ deposits also downregulate and redistribute aquaporin-4 channels[41]; however, inconsistent results have been reported in the human cerebral cortex[44].

Neuroinflammation may also play an important role in ARIA. Some researchers believe that ARIA is a type of CAA-ri based on their similar clinical manifestations, risk factors (such as the *APOE ε4* allele), and neuroimaging features[46,47]. Pathological examinations of the brains of CAA-ri patients revealed that microglia, T cells, and Aβ-containing multinucleated giant cells accumulate around the amyloid-laden vessels, suggesting the occurrence of a spontaneous anti-Aβ autoimmune response[46]. In addition, anti-Aβ autoantibodies are specifically increased in the cerebrospinal fluid and directly correlate with Aβ mobilization during the acute phase of CAA-ri[48]. Immunosuppressive treatment helps to improve symptoms[47], which further supports the hypothesis that the pathogenesis of CAA-ri is likely mediated by a selective autoimmune reaction against cerebrovascular Aβ. Therefore, the administration of exogenous amyloid-

targeting monoclonal antibodies probably strengthens the neuroinflammatory response and leads to vascular damage, thus mimicking the manifestations of CAA-ri.

5. Administration of ARIA

5.1. Severity classification

According to the prescribing information of aducanumab[49], the severity of ARIA-E or ARIA-H can be classified into three categories on MRI: mild, moderate, and severe. Mild ARIA-E shows FLAIR hyperintensity confined to the sulcus and/or cortex/subcortical white matter in one location, with a diameter <5 cm. Moderate ARIA-E requires a diameter of FLAIR hyperintensity of 5–10 cm or more than one site of involvement, with each measuring <10 cm. Severe ARIA-E requires FLAIR hyperintensity that measures >10 cm and often requires substantial subcortical white matter and/or sulcal involvement; moreover, the lesions are likely to involve one or more separate sites. The classification of ARIA-H is based on the number of lesions. Specifically, mild ARIA-H (microhemorrhage) is defined by ≤4 newly discovered microhemorrhages, the moderate type requires 5–9 newly discovered microhemorrhages, and the severe type is defined by ≥10 new microhemorrhages. Moreover, the number of local areas of superficial siderosis required to define the three types of ARIA-H (superficial siderosis) is 1, 2, and >2, respectively. Notably, the aforementioned standards are based on foreign recommendations, and Chinese experts may need to modify the standards by adapting them to the actual situation after accumulating some experience.

5.2. ARIA monitoring

At present, there are no clinical practice guidelines for the management of ARIA. Aducanumab is the only amyloid-targeting monoclonal antibody approved by the FDA; thus, the present consensus also refers to the prescribing information of aducanumab[49]. Before starting treatment, clinicians should obtain the latest baseline brain MRI scans of each patient so that clinical evaluations and comparisons can be made with the follow-up images after the medication has been taken. After treatment initiation, the clinician should obtain brain MRIs before the seventh (first dose of 10 mg/kg) and twelfth (sixth dose of 10 mg/kg) infusion of aducanumab to look for the presence of asymptomatic ARIA. It is suggested that clinicians should be extra vigilant for ARIA during the first eight infusions of aducanumab, and especially during the titration period. If patients develop symptoms suggestive of ARIA, including headache, vomiting and/or nausea, confusion, dizziness, visual impairment, gait difficulties, ataxia, tremor, new-onset seizures, or significant, and unexpected acute cognitive decline, clinicians should immediately conduct a clinical evaluation and obtain further brain MRI scans if necessary[24]. Notably, it is recommended that the same MRI equipment be used for evaluation throughout the process and that radiologists receive ARIA-related training.

For patients with radiographic findings of ARIA, enhanced clinical vigilance is recommended. Additional MRI scans may be considered if clinically indicated. If radiographically severe ARIA-H is observed, treatment may be continued with caution only after a clinical evaluation is completed and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H). For ARIA-E or mild/moderate ARIA-H, treatment may continue with caution. If dosing is temporarily suspended, dosing may then resume at the same dose and titration schedule. There are no systematic data on continued dosing with aducanumab following the detection of radiographically moderate or severe ARIA. Notably, the clinical severity and subjective feelings of patients also need to be taken into account in the decision-making process. In addition, more evidence is needed to be able to assess the correlations between imaging findings and clinical symptoms.

6. Conclusion

Although controversy exists regarding the effectiveness of aducanumab[50-52], we believe that aducanumab represents a good start for future disease-modifying therapies. For example, the approval of tacrine paved the way for the subsequent approval of other cholinesterase inhibitors, although the use of tacrine has now been abandoned. Thus, in the near future, an increasing number of specific anti-Aβ immunotherapies are likely to be approved[17,20]. At present, the application of amyloid-targeting monoclonal antibodies should be carried out in a tertiary medical center with a lot of clinical experience with AD because ARIA is an unavoidable adverse event. Clinicians and radiologists should be familiar with ARIA, and it is very important that different departments jointly diagnose and manage diseases. Most of the current data about ARIA come from Western countries, and whether these data can be directly translated to the Chinese context warrants further research. Although the present consensus fills the knowledge gap of ARIA in China, it will need updating at some point in the future, once a modified research data or management protocol has been proposed.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Introduction to "Pre-AD Alliance of China"

The "Pre-AD Alliance of China", initiated by Xuanwu Hospital and made up of 94 hospitals from 50 sites in China, aims to assess the diagnostic application of imaging in different stages of the cognitive continuum. The writing committee from the "Pre-AD Alliance of China" includes:

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