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MR in the new era of Therapeutics for Alzheimer's Disease

In this new era, MRI will be a mainstay of eligibility determination, adverse event monitoring, and disease tracking. Hence, it is a critical modality that needs further development toward optimal prediction and monitoring of newly relevant features of parenchymal and cerebrovascular structure in patients treated for AD.

Dr. James B. Brewer, MD, PhD *Professor & Chair, Department of Neuroscience, University of California - San Diego*
Suchandrima Banerjee, PhD *Senior Director - Neuro MR, GE HealthCare*

In 2020, there were over 55 million people living with dementia worldwide, with an associated economic burden of $1.3 trillion USD. Alzheimer's disease (AD) is the most common form of dementia and a major contributor of death and disability to the patient with far-reaching impact to the caregiver, family and the broader society. With ~6.5 million Americans aged 65 and older living with AD, it was the 6th leading cause of death in the United States in 2022[1].

Historically, the diagnosis of AD relied wholly on clinical symptoms, which delayed diagnoses since the pathological protein accumulation that defines the disease appears to precede clinical symptoms by around two decades[2]. Such late interventions effected a limited improvement to the patient's quality of life. Advances in diagnostic technologies and in-vivo biomarker studies identified core alterations in molecular pathology that characterize and underlie AD across its long preclinical and prodromal phases. This contributed to a proposed shift in the diagnosis and characterization of the disease toward a biologically defined approach. In 2016, the A/T/N biomarker driven research framework was developed which consisted of **A**: amyloid-β biomarker (amyloid PET, CSF $A\beta_{42}$ or $A\beta_{42}/_{40}$ ratio), **T**: tau pathology biomarker (CSF p-tau or tau PET), and **N**: neurodegeneration or neuronal injury (CSF total tau, [^{18}F]FDG-PET, or structural MRI)[3].

Concurrently, randomized clinical trials using monoclonal antibodies that target amyloid-β were being conducted to evaluate their potential for delaying progression of AD. Early studies demonstrated the ability of immune approaches to remove amyloid-β from the brain, though without clinical benefit and with a consistent and counter-intuitive acceleration of brain atrophy as measured by longitudinal volumetric MRI**.** Furthermore, patients randomized to treatment arms had an outsized share of MRI findings as revealed by regular scheduled imaging and most often appearing without associated symptoms. These were suggestive of fluid extravasation from cerebrovasculature within the brain parenchyma or sulcal leptomeningeal regions, resembling edema or effusions on T2-weighted imaging and sensitively detected by T2 FLAIR, or as micro- or macro-hemorrhages visible on long gradient-echo recalled/T2* imaging and sensitively detected by susceptibility weighted (SW) MR imaging. While also observed in AD patients as spontaneous occurrences, such as in placebo arms and outside of treatment trials, consistent evidence mounted that these findings were particularly associated with monoclonal therapies directed at removing amyloid-β. These imaging findings ranged from mild, asymptomatic, and resolving spontaneously with a temporary pause in treatment, to severe, recalcitrant, and fatal, and were termed amyloid-related imaging abnormalities (ARIA). ARIA-E refers to the appearance of fluid and edema, and ARIA-H refers to the appearance of hemosiderin and blood products. Targeted reviews on the pathobiology of ARIA-E and ARIA-H and the increased incidence in ApoE ε4 carriers are available and emerging in the extant literature[4].

Recent clinical trials using monoclonal antibodies demonstrated reduction of amyloid burden as well as delaying cognitive decline in patients along with the associated risks of ARIA[5]. The purpose of this white paper is to forecast the evolving role for MRI in the clinical care of AD patients as we enter the era of approved, disease-modifying AD therapeutics, and in particular,

pharmaceuticals that target amyloid-β removal, and that thereby increase the risk and prevalence of ARIA-E and ARIA-H. In this new era, MRI will be a mainstay of eligibility determination, adverse event monitoring, and disease tracking. Hence, it is a critical modality that needs further development toward optimal prediction and monitoring of newly relevant features of parenchymal and cerebrovascular structure in patients treated for AD. Here we anticipate modifications to clinical processes related to adverse event monitoring and disease progression; and suggest areas of opportunities.

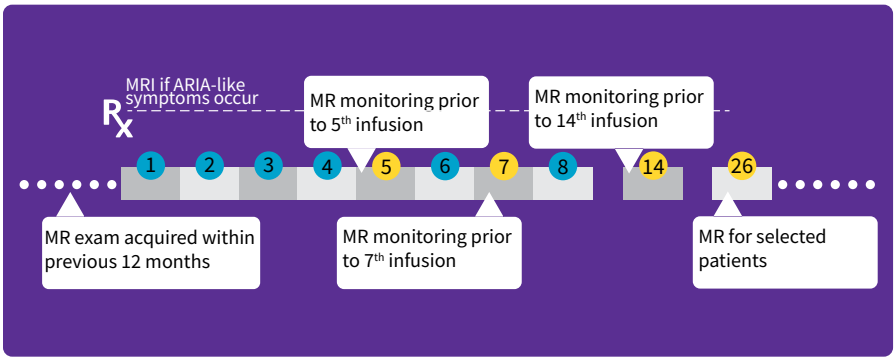

Figure 1 - Timescale view of required MRI monitoring examinations relative to Aβ therapeutic infusions. Dots represent infusions; colored blocks represent 14 calendar days per block. Adapted from Cummings J, et al. J Prev Alzheimers Dis. 2023;10(3):362-77.

One such disease modifying therapeutic was granted full approval by FDA with recommendations to obtain a recent (within one year) brain MRI prior to initiating treatment to evaluate for pre-existing ARIA and establish a baseline; and to obtain an MRI prior to the 5th, 7th, and 14th infusions[6,7]. In cases of radiographically observed ARIA occurences, treatment recommendations are based on type, severity, and presence of symptoms. Additional MR scans are also recommended for patients exhibiting ARIA or experiencing symptoms, as indicated in **Figure 1.** Symptoms associated with ARIA may overlap considerably with pre-existing benign conditions (e.g. headache) or those associated with underlying disease (e.g. confusion). Thus far, the only available test or procedure to detect ARIA, a potentially life-threatening iatrogenic condition, is MRI. Hence, in patients undergoing AD amyloid-β lowering therapy, rapid availability of MRI will be called for in emergency settings for symptoms that would otherwise elicit a low index of suspicion for serious disease. To avoid expensive and compounded disruption to patient flow and patient safety in Emergency Department (ED) and urgent care settings, ready access to brief, targeted neuroradiology protocols within the MRI modality and with rapid turnaround will be required. These emergency MRI protocols, with a sought-after trajectory for ubiquity and speed akin to the early era of CT, will need to also account for the possibility of an ischemic event in these patients, as many of the symptoms of ARIA, including focal deficit, mimic those of cerebrovascular ischemia. Further, the risk-benefit of delivering or not delivering a thrombolytic to a patient on amyloid-β lowering therapy is an area of much hand wringing for ED physicians and neurologists, particularly in light of the reported fatal cerebral hemorrhage in such a patient upon receiving thrombolytic therapy for a presumed stroke[8]. Confirmation of active ischemia and expected extent of cerebral tissue loss through rapid, emergent MRI would at least be helpful to inform such decision-making beyond what CT provides in the current stroke-code workflow. Such confirmation may also inform risk-benefit decision-making regarding anticoagulating patients on amyloid-β lowering drugs who present to the ED potentially decompensating from suspected cerebrovascular thrombosis, pulmonary embolism, or other thromboembolic disease.

Healthcare professionals are also trying to understand the implications to the non-urgent, ambulatory clinical workflow of AD patient management as they prepare for increased demand for imaging-based inclusion and specialized monitoring for ARIA. Lack of knowhow and specialty expertise will lead to disparities in care and safety in delivering amyloid-β lowering therapies across the breadth and diversity of healthcare ecosystems in the U.S. and world. This disparity exposes an urgent need for new tools to simplify the detection of ARIA at baseline and followup.

To ensure consistent detection of ARIA pathology in MR images, scan protocols should ideally be harmonized and standardized across vendors for each field strength, and every MR scanner needs to be equipped with the basic capabilities to run the ARIA monitoring protocol. Initiatives such as the American Society of Neuroradiology consensus recommendation are already underway to assist in such standardization[9]. Since many sites routinely use predominantly volumetric sequences for brain MR exams, there is an interest to include additional 3D FLAIR and susceptibility weighted sequences for ARIA monitoring in addition to the 2D T2 FLAIR and T2* gradient recalled echo (GRE) sequences employed in the clinical trials. However, this requires further consideration. For example, higher spatial resolution 3D susceptibility weighted (SW) images have a greater sensitivity to microhemorrhages. As a result, re-calibration of mild/moderate/severe criteria for ARIA-H might be required when dosing and treatment decisions are based on the 3D SW instead of 2D T2* GRE.

MR scan acceleration techniques, powered by deep learning (DL) can help shorten the targeted protocols to less than 3 minutes for 2D only and to less

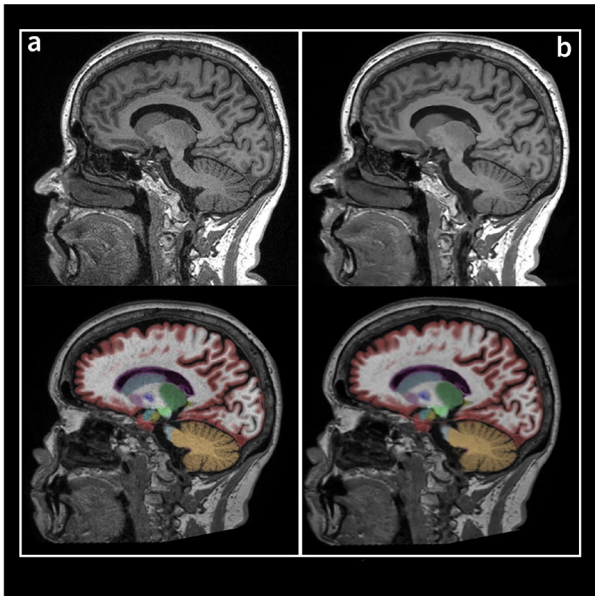

Figure 2 1mm isotropic 3D T1 MP-RAGE images **a)** 5:09 acquisition using parallel imaging (PI) and reconstructed with conventional techniques; and **b)** rapid 2:56 protocols using PI and compressed sensing (CS), and reconstructed with a Deep Learning Reconstruction technique. Noise and ringing are evident on images using the conventional reconstruction and are much reduced in the DL image even though the scan time is much shorter. Adapted from Lebel et.al, ISMRM 2022[21]

than 15 minutes when the additional 3D sequences are incorporated, while maintaining image quality, as seen in an example in **Figure 2**. Workflow simplification tools such as automated scan prescription can ensure consistent image localization in every follow-up visit, even for 2D sequences, removing the inconsistencies due to variability in patient setup and operator experience level. Protocol and prescription standardization, including new approaches enabled by AI, help mitigate demands on an overburdened radiological workforce. Further, semi-automated image assessment can help equalize adverse event read quality despite regional heterogeneity in neuroradiological expertise and training. Recognizing the inefficiency, high cost, and low penetration of training programs for introducing practicing radiologists to changes in the field, the goal of adopting new AI tools in MR neuroradiology would be to ensure that every center, equipped through the most innovative, automated, and intuitive tools as enabled through OEM vendor support, would be able to administer these drugs safely.

Beyond detection of side-effects, treating physicians referring for regular longitudinal imaging will want to derive as much information as possible from these scan sessions and resulting images, given the expense and inconvenience of obtaining them in a cognitively impaired population. Considering the A/T/N framework described above, as amyloid-β is removed from the brain and falls to floor levels, with expectation that it would not reaccumulate for perhaps decades, the treating physician is left with **N+** and **T+** biomarkers, which track one another with similar spatial pattern[10]. Of these, the marker most readily available, given required and presumably reimbursable repeated imaging, is **N+** through MRI. To maximize the value of these repeated images, quantitative structural imaging, including volumetric and promising new predictive structural markers based on diffusion would be valuable to collect in tracking disease trajectory and informing therapeutic effect[11]. The **N+** marker can be derived from a three-dimensional structural MRI scan that is routinely used in clinical practice to exclude structural abnormalities such as brain tumors, infarction, or hydrocephalus. It has the benefit of being agnostic to proteomic basis for neurodegeneration, and thus provides information to the provider about whether continued clinical decline in the absence of amyloid, as was seen in all amyloid-β treatment trials, might have led to altered trajectory from the standpoint of progressive and continued neurodegeneration and/or fluid compartment changes. Quantitation of structural anatomy is now a neuroradiology offering that most cognitive/behavioral neurologists and dementia specialists have come to expect. Reporting on these previously ignored features and improving on longitudinal measures of structural volumetric change in patients with neurodegenerative disease will be an imperative in the era of AD modulating therapeutics. Longitudinal tracking of brain volume changes with MR might help shed light on the pseudoatrophy effects reported with the anti-amyloid AD therapies. With amyloid-β at floor, an MR-based **N+** marker may become the signal to follow to determine when to finally cease or hold the expensive and burdensome infusions, which are as frequent as every two weeks.

To ensure maximal value from repeated MR imaging in this cognitively impaired population, the structural MRI will benefit from three-dimensional motion correction and cross platform harmonization directed toward optimal quantification[12]. Today, there are several postprocessing software tools commercially available for extracting brain volumetric measures from structural MRI[13]. While in the past, inter- and intra-scanner variability have been some of

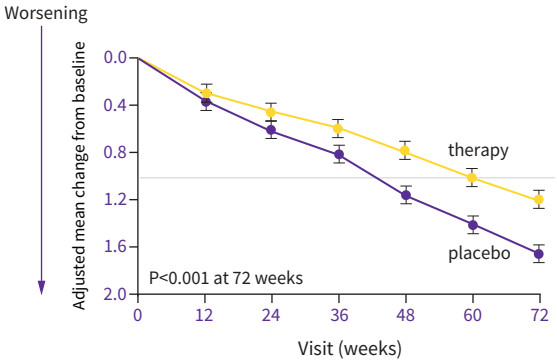

Figure 3A Slowing of cognitive decline observed with an AD therapy at the conclusion of the third phase of the Clarity AD clinical trial at 72 weeks compared to baseline on the Clinical Dementia Rating-Sum of Boxes (CDR-SB; range 0-18), with higher scores indicating greater impairment. Adapted from van Dyck CH, et al. NEJM. 2023 Jan 5;388(1):9-21.

	Therapy	Placebo
Amyloid Burden on PET (centiloids)	-59.1	0
ARIA-E (symptomatic)	12.6% (2.8%)	1.7% (0%)
ApoE ε4 carrier	15.8%	2.3%
ApoE ε4 non carrier	5.4%	0.3%
ARIA-H	17.3%	9.0%
ApoE ε4 carrier	11.9%	4.2%
ApoE ε4 non carrier	19.7%	11.3%

Figure 3B The reduction of amyloid burden at 72 weeks compared to baseline and the ARIA adverse effects from the therapy are shown. Adapted from van Dyck CH, et al. NEJM. 2023 Jan 5;388(1):9-21.

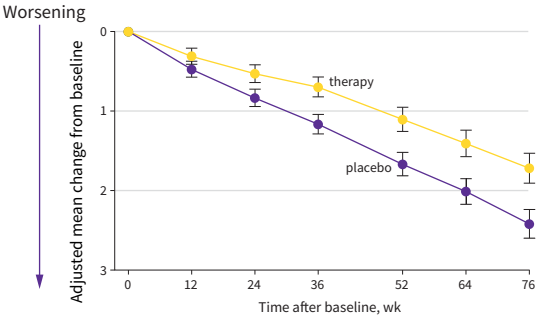

Figure 4A Slowing of cognitive decline with an anti-amyloid therapy reported at the conclusion of the TRAILBLAZER phase 3 clinical trial at 76 weeks compared to baseline on the Clinical Dementia Rating–Sum of Boxes (CDR-SB; range, 0 to 18, with higher scores indicating greater impairment). Adapted from Sims JR, et al. JAMA. 2023 Aug 8;330(6):512-27.

	Therapy	Placebo
Amyloid Burden on PET (centiloids)	-87.0	0
ARIA-E (symptomatic)	24.0% (6.1%)	1.9% (0.1%)
ApoE ε4 carrier	27%	1.7%
ApoE ε4 non carrier	15.7%	0.8%
ARIA-H	31.4%	13.6%
ApoE ε4 carrier	36.6%	14.0%
ApoE ε4 non carrier	18.8%	11.2%

Figure 4B The reduction of amyloid burden at 76 weeks compared to baseline reported at the conclusion of the TRAILBLAZER phase 3 clinical trial and the ARIA adverse effects from the anti-amyloid therapy are shown. Adapted from Sims JR, et al. JAMA. 2023 Aug 8;330(6):512-27.

their pitfalls, use of DL has significantly improved their repeatability in recent years. On the microstructural imaging front, recent works demonstrated the potential of advanced diffusion metrics such as Restricted Spectrum Imaging (RSI), which measures of gray and white matter microarchitecture, to be associated with cognitive decline, and mean restricted diffusion in the medial temporal lobe to be correlated with rates of cognitive decline and progression of dementia severity[14,15]. Such techniques will enhance precision of measurement across longitudinal scans and will be important to markedly increase the informative value of quantitative assessments of structure, whether through volumetry or powerful new diffusion measures of local neurite density. Removal of amyloid-β will help unmask the underlying vascular features and non-amyloid proteinopathies that are leading to heterogeneous rates of continued cognitive decline, and the availability of improved quantitative MR as a ubiquitous biomarker will be critical in characterizing this process[16].

Future directions

It is now well established that vascular dysfunction accompanies/contributes Alzheimer's disease and the disruption of the blood brain barrier (BBB) also plays a role[17,18]. While the standard technique for assessing BBB permeability is by the measurement of the volume transfer coefficient by dynamic contrast enhanced MRI, most of the routine brain MR protocols used in mild cognitive impaired cohorts are done without a contrast injection[19]. Early work on non-contrast-enhanced BBB assessment using diffusion and non-contrast perfusion methods have been reported in the literature. Maturation of such techniques would greatly help in understanding at what stage of the AD continuum the BBB disruption happens and its correlation with microstructural changes[20].

To summarize, MR will play a pivotal role in appropriate administration of anti-amyloid AD therapy to patients, and AI-driven MR acceleration and consistency tools and automated ARIA assessment will be needed to accommodate the anticipated increased burden on the clinical workflow. MRI tools for evaluating vascular brain integrity can potentially aid in better risk stratification of patients likely to develop ARIA in response to therapy and can inform personalized dose management. The non-ionizing nature of MRI and its versatility makes it ideal for longitudinal tracking of brain changes; and advanced quantitative techniques offer potential to advance understanding of the sequence of microstructural, vascular and permeability changes in early stages of AD as well as throughout the care pathway.

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