MRI in the new era of antiamyloid mAbs for the treatment of Alzheimer's disease

Massimo Filippi[a,b,c], *Giordano Cecchetti*[a,b,c] *and Federica Agosta*[a,b,c]

Purpose of review
Currently, three antibeta amyloid (Aβ) mAbs are approved or under examination in USA and in Europe for the treatment of patients with early Alzheimer's disease. The aim of this review is to summarize the role of MRI in the mandatory redefinition of dementia care.

Recent findings
Disease-modifying therapies require a reliable biological diagnosis of Alzheimer's disease. Structural MRI should be acquired at the beginning of the diagnostic process as a gateway before subsequent etiological biomarkers. MRI findings, indeed, may support a diagnosis of Alzheimer's disease or suggest alternative non-Alzheimer's disease conditions. Given the high risk/benefit ratio of mAbs and the impact of amyloid-related imaging abnormalities (ARIA), moreover, MRI will be crucial for the appropriate patient selection and safety monitoring. Ad-hoc neuroimaging classification systems of ARIA have been developed and continuous education of prescribers and imaging raters is prompted. MRI measures have been also assessed in clinical trials as potential markers of therapeutic efficacy; results, though, are controversial and still need clarification.

Summary
Structural MRI will play a crucial role in the upcoming era of amyloid-lowering mAbs against Alzheimer's disease, from the correct patient selection to the monitoring of adverse events and of disease progression.

Keywords
Alzheimer's disease, amyloid, amyloid-related imaging abnormalities, mAbs, MRI

INTRODUCTION

Alzheimer's disease is the leading cause of dementia worldwide, affecting 55 million people in 2019 [1]. After more than a century since the first description of distinct clinical and neuropathological correlates of Alzheimer's disease, encouraging results of clinical trials testing antiβ amyloid (Aβ) mAbs have been achieved [2–4]. Currently, three anti-Aβ mAbs have been approved or are under examination for accelerated approval in the United States and in Europe for the treatment of patients with early Alzheimer's disease [5,6▪].

In such a scenario, the increasing need for a reliable etiological diagnosis of Alzheimer's disease has led to the grouping of already available and possible future neuroimaging biomarkers into three main categories based on the information they provide [7]: biomarkers of Aβ plaques (A: amyloid-PET), biomarkers of fibrillar tau (T: tau-PET) and biomarkers of neurodegeneration (N: atrophy on MRI, FDG-PET hypometabolism). This framework allows, in case of both 'A' and 'T' abnormalities, the application of the label 'AD' in any person within a continuum from normal cognitive functioning to full-blown dementia and regardless of specific clinical presentations (i.e. typical amnestic or atypical Alzheimer's disease syndromes) [7]. Biomarkers in the N group provide additional indications for staging severity, despite being unspecific for Alzheimer's disease [7]. Apart from the A/T/N scheme, imaging biomarkers could be practically categorized based on clinical aim [8,9▪]: etiological definition (i.e. the presence of a specific disease), staging and monitoring of disease progression. In

[a]Neurology Unit, [b]Neuroimaging Research Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute and [c]Vita-Salute San Raffaele University, Milan, Italy

Correspondence to Massimo Filippi, MD, FEAN, FAAN, Full Professor of Neurology, Vita-Salute San Raffaele University, Chair, Neurology Unit, Chair, Neurorehabilitation Unit, Director, Neurophysiology Service, Director, MS Center, Director, Neuroimaging Research Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Via Olgettina, 60, 20132 Milan, Italy. E-mail: filippi.massimo@hsr.it

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KEY POINTS

- The introduction of an effective disease-modifying treatment for Alzheimer's disease requires an enormous change in the delivery of dementia care.
- Structural MRI is a crucial tool for the appropriate patient selection and in the monitoring of amyloid-related imaging abnormalities (ARIA).
- Ad-hoc MRI classification systems of ARIA have been developed to guide clinicians with the correct management strategies.
- Controversial results from clinical trials suggest that the use of structural MRI as a measure of efficacy of antiamyloid antibodies still needs clarification.

such terms, both amyloid- and tau-PET allow to assess the presence and the extension of Alzheimer's disease, whereas structural MRI and FDG-PET (but also tau-PET) are topographic biomarkers, resembling neuronal and synaptic loss, and thus empowering staging and prognosis.

The advent of Aβ-lowering mAbs, with such a high risk–benefit ratio, necessarily requires additional considerations on biomarkers, regarding the correct patients selection and the monitoring of efficacy and side effects [6▪,10▪]: after establishing the presence and the extent of Alzheimer's disease neuropathology and the risk for clinical progression at prodromal stages, indeed, a thorough neuroimaging exclusion criteria assessment, the monitoring of neuroimaging efficacy outcomes and the surveillance over amyloid-related imaging abnormalities (ARIA) must be dispensed.

MRI biomarkers encompass a range of techniques at different stages of validation [9▪,11]: structural MRI, showing the greatest evidence in terms of clinical use, and advanced analysis of diffusion MRI or resting-state functional MRI sequences, still under development for the application at the single subject level. Structural MRI, actually, is the most widely used in specialized clinical settings and recognized as a valid support for clinical diagnosis and monitoring of progression; furthermore, in light of the advent of disease-modifying therapies for Alzheimer's disease, it has progressively emerged as a crucial tool for correct patient's selection and for monitoring of ARIA [10▪,12,13].

While acknowledging the need for a continuous research on the validation of recent or future etiological biomarkers of Alzheimer's disease, the aim of this dissertation is to summarize the role of structural MRI in the era of amyloid-lowering mAbs for the treatment of early Alzheimer's disease.

MRI AS A VALID SUPPORT FOR A RELIABLE DIAGNOSIS OF ALZHEIMER'S DISEASE

There is wide consensus about the usefulness of structural neuroimaging [(i.e. brain computed tomography (CT) or MRI] as the first step of diagnostic process in cognitive decline, after clinical and neuropsychological evaluations and before other neuroimaging techniques directed at establishing the presence of Alzheimer's disease pathology [11,14,15]. Brain MRI allows the exclusion of alternative or concomitant causes that might underly the disturbances of the patient and that could require specific treatments, such as cerebrovascular disease, normal pressure hydrocephalus or tumours.

In addition, MRI is able to unravel the presence of specific atrophy patterns widely recognized as being associated with different neurodegenerative conditions [16]. When speaking of typical amnestic late-onset presentation of Alzheimer's disease, specifically, atrophy is expected in the hippocampal areas even before the occurrence of cognitive symptoms, and before spreading to the posterior cingulate/precuneus areas and to temporal, lateral parietal, frontal and eventually occipital cortical regions [8,9▪,17]. A relatively recent strategic roadmap, summarizing conclusions and recommendations of interdisciplinary academic experts on the use of biomarkers for the diagnosis of Alzheimer's disease, showed that visual rating and volumetric assessment of medial temporal atrophy have indeed achieved analytical and clinical validity, albeit prerogative only of specialized memory centres [11]. Taking this as a starting point, deep learning algorithms were trained to automatically predict individual diagnoses of dementia and mild cognitive impairment due to Alzheimer's disease based on a single brain structural MRI scan [18]. Hippocampal atrophy, though, is not sensitive to Alzheimer's disease, as it could be found in other conditions, such as limbic-predominant TDP-43 encephalopathy (LATE), epilepsy and even in normal ageing [19,20]. Similarly, precuneus/posterior cingulate degeneration was demonstrated in nondemented elderly individuals with Apolipoprotein E (ApoE) haplotype ε4 [21]. Moreover, atrophy is not homogeneous among atypical clinical presentations of Alzheimer's disease, showing association to syndrome-specific clinical features. In early-onset Alzheimer's disease (age at onset < 65 years), it is usually more severe and more diffuse, involving hippocampus, temporal lobes, precuneus, cingulate gyrus and frontal cortex since the initial phases [22]; posterior cortical atrophy shows predominant occipito-parietal or occipito-temporal atrophy [23]; the logopenic-variant of primary progressive aphasia

displays predominant left posterior perisylvian and/or temporoparietal junction degeneration [24]; eventually, the behavioural variant of Alzheimer's disease typically shows a greater involvement of prefrontal and temporal areas than typical Alzheimer's disease, but still greater degeneration of posterior cortical areas than the behavioural variant of fronto-temporal degeneration [17].

Thus, MRI has limited specificity for Alzheimer's disease when used alone; when taking into account also clinical and neuropsychological features, though, it is a useful initial gateway for subsequent assessments, helping in deciding if other biomarkers should be explored next and which [14].

AMYLOID-RELATED IMAGING ABNORMALITIES RISK AND MONITORING

After establishing a reliable etiological diagnosis of Alzheimer's disease and excluding the presence of significant neurological and extra-neurological comorbidities, a correct profiling of patients more suitable for an immunotherapy initiation necessarily requires a multidisciplinary approach and an extensive clinical-instrumental evaluation for the definition of a personalized composite risk/benefit ratio, in which MRI exerts an essential role [6▪].

Current evidence suggests a significant impact of ARIA on treatment regimens with anti-Aβ mAbs. ARIA is a general term, which covers two classes of MRI signal alterations that are consequence of immunotherapy: ARIA with oedema and effusion (ARIA-E) and ARIA with haemosiderin deposits (ARIA-H) (Fig. 1). ARIA-E refers to parenchymal oedema and sulcal effusion, which commonly manifest as transient hyperintensities on fluid attenuated inversion recovery (FLAIR) or T2-weighted MRI sequences, with no restriction on diffusion-weighted imaging (DWI). ARIA-H refers to deposits of haemosiderin, including parenchymal microhaemorrhages and leptomeningeal superficial siderosis, which manifest as very low intensity signals detected on T2$*$ gradient recalled echo (GRE) or susceptibility-weighted imaging (SWI) MRI sequences [10▪]. ARIA-E and ARIA-H are thought to result from an increased vascular fragility and leakage of proteinaceous fluid and erythrocytes due to mAbs therapeutic effect.

MRI allows not only to detect ARIA after treatment initiation, but also to ponder the well established risk factors for ARIA before treatment and to decide whether to prescribe or not an immunotherapy [10▪]. Among risk factors, indeed, MRI signs of cerebral amyloid angiopathy and pronounced cerebrovascular disease at baseline should be carefully accounted for [25]. Specifically, recent recommendations of academic experts for the appropriate use of aducanumab report the MRI exclusionary criteria [13]: any acute or subacute haemorrhage, any macrohaemorrhage, any cortical infarction larger than 1.5 cm, one lacunar infarction larger than 1.5 cm, more than four microhaemorrhages, more than one area of superficial siderosis and extensive white matter disease indicative of ischaemic injury. MRI should be acquired within 1 year before the first treatment administration and appropriate MRI sequences at baseline should include T1, T2 or FLAIR, GRE or preferably SWI sequences, and DWI [13]. Recommended field strength should be of at least 1.5 T [10▪].

ARIA incidence is greater in ApoE haplotype ε4 carriers and at higher treatment dosages during the first weeks of treatment, likely due to a higher mobilization of parenchymal amyloid towards cerebral vessels [10▪]. ARIA occurrence is further associated with pharmacodynamic properties of anti-Aβ mAbs, showing lower rates in trials testing mAbs selectively targeting β-amyloid soluble conformations (i.e. lecanemab). ARIA-E emerged indeed as a frequent finding in high-dose aducanumab EMERGE and ENGAGE phase-3 trials (35–36%) [2] and in donanemab TRAILBLAZER-ALZ phase-2 and phase 3 trials (25.4–26.7%) [3,26], whereas a lower rate of ARIA-E was detected in lecanemab Clarity Alzheimer's disease phase-3 trial (12.6%) [4]. Predefined MRI monitoring plans are therefore crucial in the era of amyloid-lowering agents. As ARIA are clinically undetectable in many cases (∼3–10% of symptomatic ARIA across different mAbs) and occur early during treatment, it is advisable to acquire MRI scans at specific timepoint after the first administration of anti-Aβ mAbs. According to abovementioned expert recommendations for the appropriate use of aducanumab, for example, MRI should be acquired before uptitration at the fifth and at the seventh doses and then before the ninth and the 12th doses [13]. Similarly, prescribing information of lecanemab by U.S. Food and Drug Administration (FDA), commend to obtain a MRI prior to the fifth, seventh and 14th infusions [27]. In addition to predefined scans, MRI should be also acquired at any time if symptoms suggestive for ARIA appear (i.e. headache, dizziness, confusion or any neurological focal sign/symptom).

Moreover, it is not only a matter of when to perform a MRI, but also of how to interpret images: robust and validated MRI scoring systems are therefore critical monitoring tools for the detection of these events [10▪]. The Barkhof Scale is a well known 60-point scoring system for ARIA-E, widely used in clinical trials testing anti-Aβ agents. The score is obtained by summing the individual extension

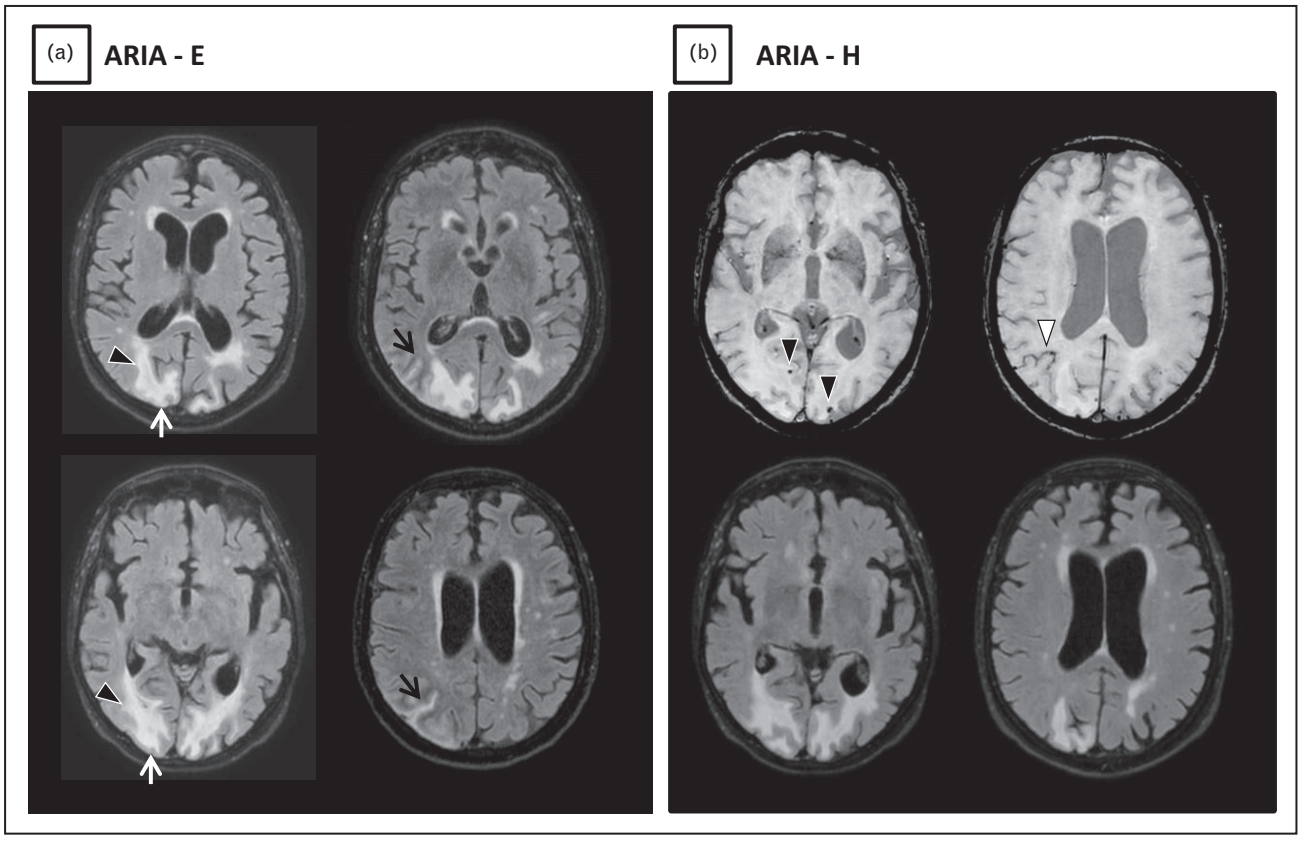

FIGURE 1. MRI features of ARIA-E and ARIA-H. Left: axial fluid-attenuated inversion recovery (FLAIR) images show ARIA-E features in a female 72-year-old patient diagnosed with prodromal Alzheimer's disease and enrolled in a clinical trial testing ab-amyloid lowering agent. They show parenchymal (black arrowheads) and sulcal (black arrows) hyperintensities involving subcortical and deep white matter in occipital and parietal lobes, associated with gyral swelling (white arrows). Right: axial susceptibility-weighted images (SWI) (upper line) and FLAIR (lower line) images in the same patient. SWI images show hypointense dotted areas consistent with micro-haemorrhages (black arrowheads) and a hypointense subarachnoid signal (white arrowhead) consistent with superficial siderosis. ARIA-E, amyloid-related imaging abnormalities with oedema and effusion; ARIA-H, amyloid-related imaging abnormalities with haemosiderin deposits. Reproduced with permission from [10▪].

scores of 12 brain regions [28,29]. More recently, simplified 3-point and 5-point scales have been also proposed, showing a good correlation with the Barkhof Scale and a good inter-rater agreement. The 3-point ARIA scoring system is based on the spatial extension of ARIA-E, which is considered mild if smaller than 5 cm, moderate between 5 and 10 cm and severe if greater than 10 cm; the 5-point scale introduces intermediate scores in consideration of the number of lesions [10▪,30]. An adapted 3-point scale, in particular, has been implemented in aducanumab and lecanemab FDA prescribing information for both ARIA-E and ARIA-H; combined with the presence/absence of ARIA-related symptoms, it is meant to guide clinicians with the decision on whether to continue treatment, or suspend it temporarily or definitively (Table 1) [27,31]. In case of radiographically mild ARIA-E with only mild or no symptoms dose may be continued; in all other cases, the treatment should be suspended. In case of ARIA-H, dose may be continued only in case of radiographically mild ARIA and no symptoms (Table 1).

MRI AS A MARKER OF THERAPEUTIC EFFECT

Rates of structural MRI measures change over time, including hippocampus, ventricular system and whole brain volumes, have been shown to correlate with changes in cognitive performances and with baseline levels of amyloid- and tau-pathology biomarkers within the cerebrospinal fluid (CSF), acting as a potential downstream biomarker of Alzheimer's disease progression [32,33]. Moreover, specific baseline MRI atrophy patterns have been shown to predict cognitive outcomes in Alzheimer's disease

Table 1. MRI classification criteria of ARIA in Leqembi FDA prescribing information

ARIA type	Radiographic severity		
	Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in one location <5 cm	FLAIR hyperintensity 5–10 cm in single greatest dimension, or more than one site of involvement, each measuring <10 cm	FLAIR hyperintensity >10 cm with associated gyral swelling and sulcal effacement. One or more separate/independent sites of involvement may be noted.
ARIA-H microhaemorrhage	≤ 4 new incident microhaemorrhages	Five to nine new incident microhaemorrhages	10 or more new incident microhaemorrhages
ARIA-H superficial siderosis	One focal area of superficial siderosis	Two focal areas of superficial siderosis	> 2 areas of superficial siderosis

ARIA-E, amyloid-related imaging abnormalities with oedema and effusion; ARIA-H, amyloid-related imaging abnormalities with haemosiderin deposits.
Table reprinted from FDA Leqembi prescribing information [27].

patients over time and to relate with CSF biomarkers of Alzheimer's disease pathology [34,35].

As a matter of fact, volumetric MRI assessments have been implemented among secondary outcomes of most clinical trials testing anti-Aβ mAbs. Despite it would have been reasonable to expect reduced rates of atrophy progression, especially in trials testing aducanumab, lecanemab and donanemab (i.e. those showing biological and/or clinical effects), structural MRI results from clinical trials are consistent in showing no effect or increased rates of brain volume loss, especially at lateral ventricles level [2–4,36]. Although these effects are consistent with results from other Aβ-lowering agents [37–39,40▪,41▪], they did not attract much attention in the context of the repeated failures of anti Aβ agents until 2021. In a recent systematic review exploring structural MRI outcomes of Alzheimer's disease clinical trials, Alves *et al.* [40▪] concluded that anti-Aβ mAbs may accelerate brain atrophy; recent evidence of long-term clinical benefit of lecanemab, together with the improvement of CSF and plasma biomarkers of neurodegeneration in treated patients, though, seem to exclude that accelerated volume loss should be read in a neurodegenerative pathway [41▪]. Beyond controversies, the reasons underlying such MRI findings are not established yet; they may be indeed index of increased neurodegeneration, but alternative explanations in terms of pseudoatrophy include Aβ-plaques bulk removal, off-target reductions in inflammatory responses and/or alterations in CSF dynamics [36,41▪]. Continuous research and longer periods of observation are necessary to put light on these findings.

CONCLUSION

The advent of anti-Aβ antibodies for the treatment of early Alzheimer's disease will prompt radical changes in dementia care supply, as they will become more and more available in clinical settings. Structural MRI will play a crucial role in all steps of the pathway, from the correct patient selection to the monitoring of adverse events and of disease progression. Despite some aspects still need clarification (e.g. increased rates of change of volumetric measures in treated patients compared with controls), current evidence highlights the significant impact of ARIA on anti-Aβ treatment regimens, supporting though the notion that treatments can be continued with careful MRI and clinical monitoring even in case of ARIA. Standardized (and likely antibody-specific) neuroradiological management protocols will necessitate continuous updates as the research on ARIA goes forward in the real world.

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Conflicts of interest

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