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ABSTRACT

SUMMARY: Amyloid-targeting therapy has recently become widely available in the United States for the treatment of patients with symptomatic mild Alzheimer disease (AD). At present, there are no biomarkers that have been clinically validated to assess treatment response in routine clinical practice; longitudinal amyloid PET could play a role but is not cost-effective. This report presents a case series of 6 patients with AD, whose amyloid positivity was confirmed by PET or CSF biomarkers, who underwent baseline and longitudinal arterial spin-labeling MR imaging (ASL-MR) as part of Food and Drug Administration–mandated, clinical standard-of-care, noncontrast MR monitoring to assess for amyloid-related imaging abnormalities (ARIA). We and others have previously reported that ASL-MR can screen for neurodegenerative disease as a proxy for FDG-PET and can be easily added on as a cost-effective, repeatable method to monitor post therapy changes. This series highlights varied CBF changes in response to lecanemab therapy. For instance, Cases 1, 3, and 5 showed increased CBF after multiple infusions, with subjective cognitive improvement in Case 1 and improved MoCA scores in Case 3. Case 2 showed improved CBF initially before the fifth infusion, but this returned to baseline in the subsequent study, with no cognitive improvement over the course of therapy. Cases 4 and 6 have demonstrated no substantial changes in regional CBF thus far on therapy, with cognitive decline in Case 4. This case series underscores the potential utility of ASL-MR as an adjunct sequence to current imaging protocols to monitor treatment response to antiamyloid therapy.

ABBREVIATIONS: Aβ = amyloid-β; AD = Alzheimer disease; ARIA = amyloid-related imaging abnormalities; ASL-MR = arterial spin-labeling MR imaging; MoCA = Montreal Cognitive Assessment

For the past year, lecanemab has been increasingly available in the United States for the treatment of symptomatic mild cognitive impairment or mild dementia due to Alzheimer disease (AD),[1] and donanemab was recently approved for the same indication.[2] To qualify for therapy, patients have to undergo amyloid PET or CSF assays[1] to confirm the presence of amyloid pathology. Lecanemab is a recombinant humanized IgG1 monoclonal antibody that targets amyloid oligomers, protofibrils, and insoluble fibrils.[3] It binds preferentially to protofibrils, which are a high molecular weight form of soluble amyloid and are a component of amyloid plaques.[3] Despite its availability, at present, there are no biomarkers that have been clinically validated to assess treatment response in routine clinical practice; longitudinal amyloid PET could play a role but is not cost-effective. While lecanemab has shown a modest impact on cognition over 18 months, slowing cognitive decline by 27%, there is minimal detectable cognitive impact in the first 6 months of treatment, and very little is known about the brain's response to therapy. Therefore, tracking the effects of early medication remains elusive for clinicians.[4]

The US Food and Drug Administration (FDA) mandates serial noncontrast MRI scans to monitor for amyloid-related imaging abnormalities (ARIA) while receiving bimonthly lecanemab treatment (before the fifth, seventh, and 14th infusions).[1] Additionally, an MRI scan at week 52 (before the 26th infusion) is suggested, particularly for apolipoprotein E ε4 carriers, who have an increased risk of ARIA, and for those who had ARIA in prior studies.[1]

Arterial spin-labeling MRI (ASL-MR) uses magnetically labeled water (ie, blood) as an endogenous tracer to measure CBF in the brain.[5-7] Unlike other perfusion imaging techniques that use ^{15}O-PET or dynamic imaging with gadolinium contrast, ASL-MR does not require an external tracer or ionizing radiation.[7] CBF, estimated by ASL-MR, is closely linked to brain

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Patient characteristics, including history of vascular risk factors

Age	Confirmation of Alzheimer Pathology	APOE Genotype	Baseline MoCA score	Hypertension	Dyslipidemia	Diabetes
77	Amyloid PET	E3/E3	23	Yes	Yes	No
59	CSF biomarkers	E3/E3	20	No	No	No
74	Amyloid PET	E3/E3	22	No	No	No
62	Amyloid PET	E3/E3	16 (MMSE 22)	No	Yes	No
79	Amyloid PET	E3/E3	21	No	Yes	No
68	CSF biomarkers	E4/E4	14 (CDR 1)	Yes	Yes	No

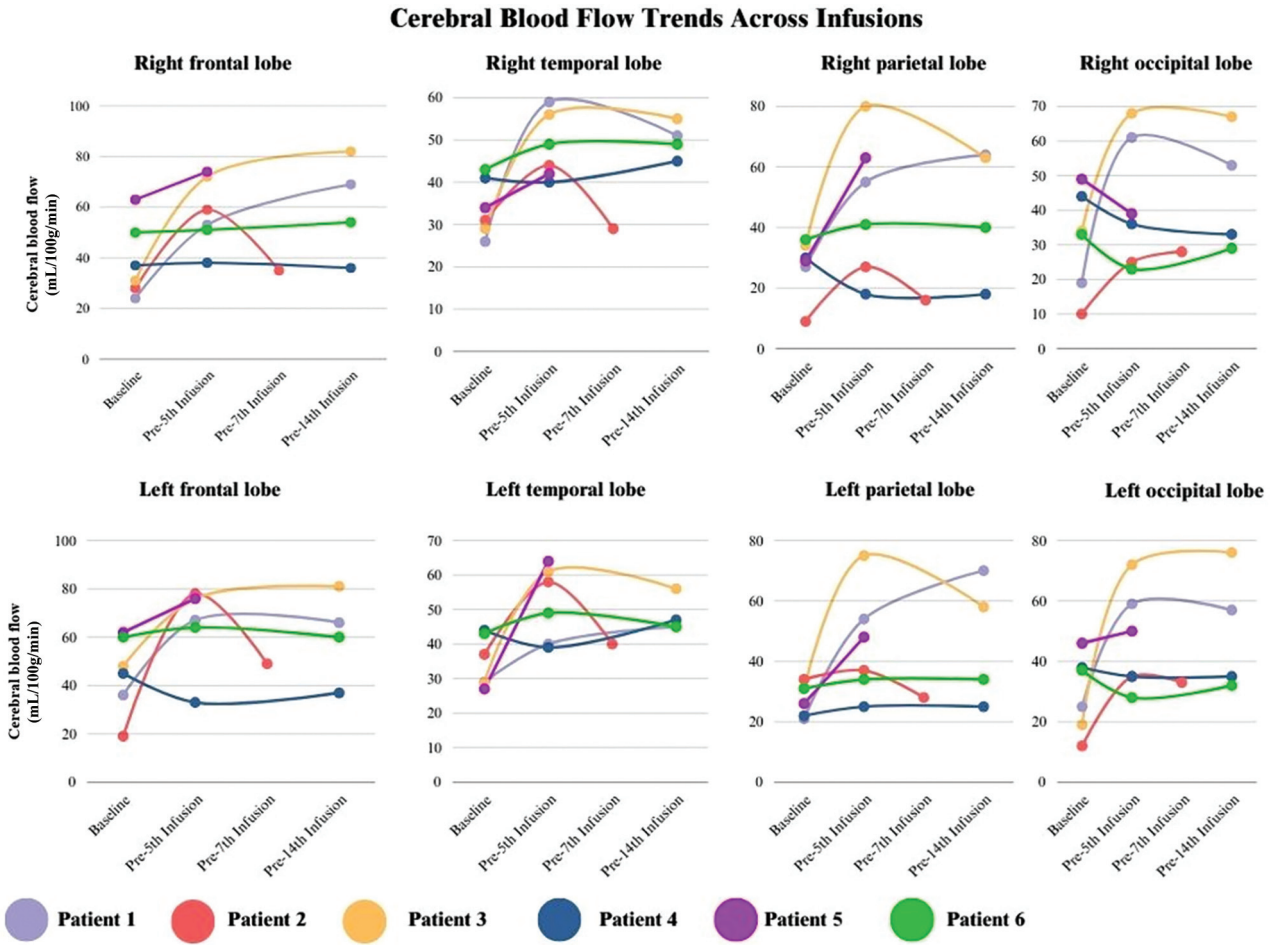

FIG 1. Line graphs showing trends in CBF values across time points. Data are shown for the 6 patients included in this case series, with measurements in the frontal, temporal, parietal, and occipital lobes, right or left.

metabolism and associates with FDG-PET, thus representing an efficient, low-cost, noninvasive, and quantitative method for evaluating brain function.[5-7]

In this report, we present 6 cases of patients with AD, whose amyloid positivity was confirmed by PET or CSF biomarkers, who underwent serial ASL-MR while on lecanemab therapy (Table). All patients were imaged on the same clinical 3T Signa Architect MRI scanner (GE Healthcare). The 3D pseudo continuous ASL-MR clinical product sequence had the following parameters: PLD 2025 ms, TR 4876, TE 53.6, 38 × 4 mm axial slices, FOV 24, matrix size 512; the scanning time was 4 minutes and 24 seconds (Supplemental Data). CBF maps were processed by using the AW Server Version 3.2 extension 4.0 (GE Healthcare), set to a range of 0–80 mL/100 g/min by using the rainbow color scheme. Images were visually interpreted in native space. Regions-of-interest were also placed on the CBF maps to assess quantitative changes over the course of therapy (Fig 1, Supplemental Data). All patients had well-controlled, stable comorbidities, and all followed treatment guidelines for initiation of therapy and monitoring. All cases were followed clinically up to the time of the writing of this manuscript, which was at least to the 14th infusion for Cases 1, 3, and 4. We hypothesized that antiamyloid therapy would lead to improved cerebral perfusion, as seen on ASL-MR, potentially due to clearance of both parenchymal and vascular amyloid.[8] Here, we present the CBF maps of these patients at baseline and while receiving lecanemab, illustrating the potential utility of ASL-MR in monitoring the effects of lecanemab on brain perfusion.

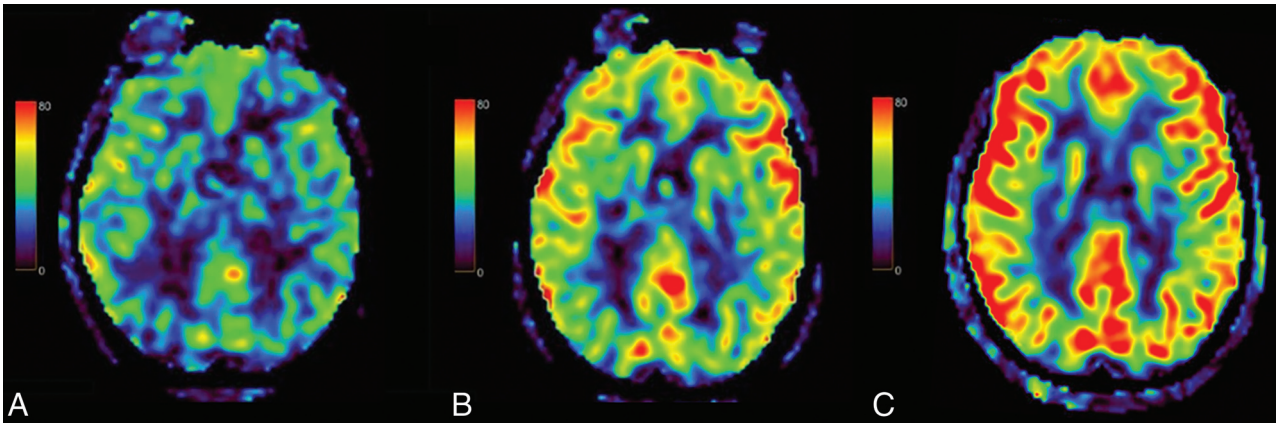

FIG 2. Patient 1 CBF maps. *A*, Baseline CBF map, before lecanemab treatment, demonstrating hypoperfusion, most prominently in the left frontal and bilateral parietal lobes. Posttreatment CBF map, obtained before the administration of the fifth dose of lecanemab (*B*), reveals a marked overall increase in cerebral perfusion in all brain regions, which increases further on the CBF map before the 14th dose (*C*).

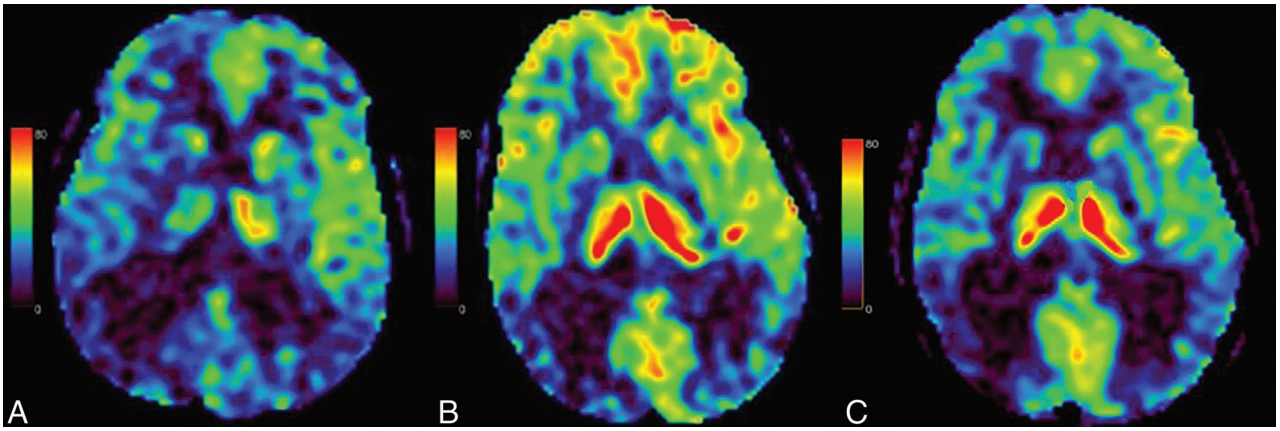

FIG 3. Patient 2 CBF maps. *A*, Baseline CBF map showing hypoperfusion in the bilateral frontal, parietal, and occipital lobes, more pronounced on the right. *B*, CBF map before the fifth dose of lecanemab, demonstrating marked improvement in cerebral perfusion, especially in the bilateral frontal lobes. *C*, CBF map before the seventh dose of lecanemab, showing decreased overall perfusion compared with the prior MRI and no substantial change from baseline.

CASE 1

A 77-year-old right-handed woman with a medical history of hyperlipidemia, hypertension, and heart failure, with an APOE Ɛ3/Ɛ3 genotype, presented with a 1.5-year history of progressive short-term memory loss, word-finding difficulty, occasional disorientation, and computer apraxia. Symptoms possibly began after parotid gland surgery, during which she experienced mild postoperative delirium. Her baseline Montreal Cognitive Assessment (MoCA) score was 23 out of 30. FDG-PET showed symmetric temporoparietal hypometabolism, a typical pattern for AD (Supplemental Data), and ASL-MR revealed decreased CBF in the left parietal and temporal lobes, as well as the bilateral frontal lobes (Fig 2). A positive amyloid PET confirmed the diagnosis of AD (Supplemental Data). She started treatment with lecanemab. ASL-MR performed at the time of the monitoring MRI scans, before the fifth, seventh, and 14th infusions, showed no ARIA and markedly improved CBF compared with baseline, most notably before the 14th infusion (Fig 2). The patient and family reported subjective cognitive improvement, although the MoCA score remained unchanged at 23/30 after 6 months of therapy. Notably, there was no change in mild volume loss or minimal burden of white matter hyperintensities over the course of therapy (Supplemental Data).

CASE 2

A 59-year-old right-handed woman presented with an 8-month history of progressive short-term memory loss, confusion, and increased anxiety. She struggled with tasks such as understanding the calendar and organizing simple work assignments. The patient had normal walking, with no shuffling or dragging of feet, and reported no urinary incontinence. Her initial MoCA score was 20/30; her APOE genotype was Ɛ3/Ɛ3. FDG-PET showed temporoparietal hypometabolism, and MRI showed marked volume loss and decreased CBF in the bilateral temporal and parietal lobes, as well as the frontal lobes (Fig 3, Supplemental Data). CSF analysis confirmed the diagnosis of early-onset AD. She began treatment with donepezil, followed by lecanemab. The patient reported feeling less anxious and more socially active, although cognitive challenges persisted. The CBF map showed marked improvement on the scan before the fifth infusion, but the CBF then decreased on the subsequent

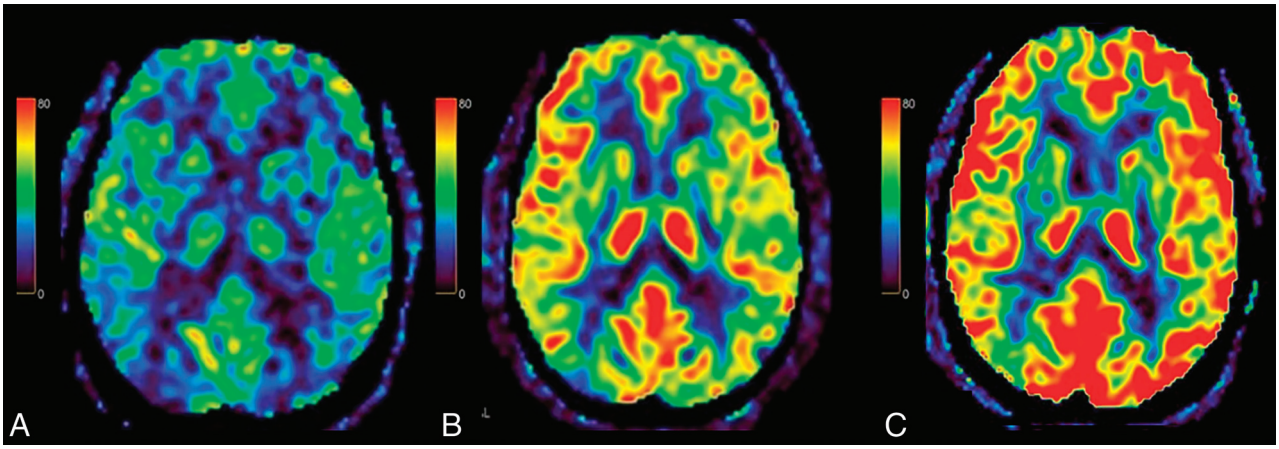

FIG 4. Patient 3 CBF maps. *A*, Baseline CBF map showing reduced cerebral blood flow in the bilateral parietal lobes, as well as the frontal lobes, to a lesser extent. *B*, CBF map before the fifth dose of lecanemab, showing improvement in blood flow in all brain regions. *C*, CBF map before the 14th dose of lecanemab, showing further increased blood flow, compared with prior monitoring and baseline CBF maps.

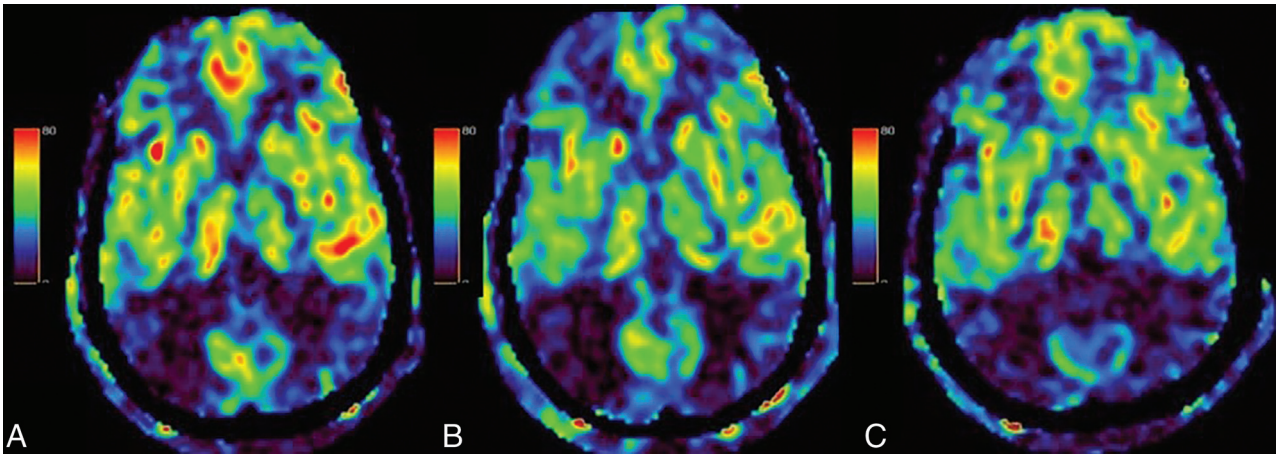

FIG 5. Patient 4 CBF maps. *A*, Baseline CBF map showing hypoperfusion in the bilateral parietal lobes, as well as the right frontal lobe, to a lesser extent. *B*, CBF map before the fifth dose of lecanemab, with no substantial change in overall cerebral perfusion compared with baseline. *C*, CBF map before the 14th dose of lecanemab again showing no notable change in cerebral perfusion compared with the previous studies.

scan before the seventh dose (Fig 3). There was no evidence of ARIA; the minimal burden of white matter hyperintensities stayed stable (Supplemental Data).

CASE 3

A 74-year-old right-handed man presented with a 10-year history of slow progressive memory decline, life-long depression, monoclonal gammopathy of unknown significance with paresthesias, prostate cancer, and sleep apnea. Three paternal relatives were reported to have a history of cognitive impairment. His baseline MoCA score was 22/30 with deficits in executive function, visuospatial tasks, and short-term recall; his APOE genotype was Ɛ3/Ɛ3. Baseline FDG-PET showed frontal hypometabolism initially favored to represent mild frontotemporal dementia, while MRI showed mild global volume loss and decreased CBF in the bilateral parietal, temporal, and frontal lobes (Fig 4, Supplemental Data). CSF biomarkers were indeterminate, but subsequent amyloid and τ PET scans were positive, confirming AD (Supplemental Data). Monitoring MRI scans before the fifth, seventh, and 14th lecanemab infusions showed no evidence of ARIA and continued improvement in CBF (Fig 4) despite no change in mild volume loss and minimal burden of white matter hyperintensities (Supplemental Data). The patient reported improved working memory and overall cognitive function; the prelecanemab MoCA score on donepezil (26/30) improved after 6 months of lecanemab therapy to 29/30.

CASE 4

A 62-year-old right-handed man presented with progressive cognitive decline over 2.5 years and worsened anxiety after a suspected COVID infection. His medical history included hypertension and concussion. Cognitive assessments revealed deficits in visuospatial organization, working memory, attention, and orientation. Neuropsychological testing indicated performance below expectation, compared with education-based norms, in multiple cognitive domains, with substantial deficits in visuoperceptual ability, working memory, and verbal fluency. His APOE genotype was Ɛ3/Ɛ3.

FDG-PET showed temporoparietal hypometabolism, and MRI showed decreased CBF bilaterally in the temporal, parietal, and frontal lobes (Fig 5). CSF biomarkers and amyloid PET confirmed

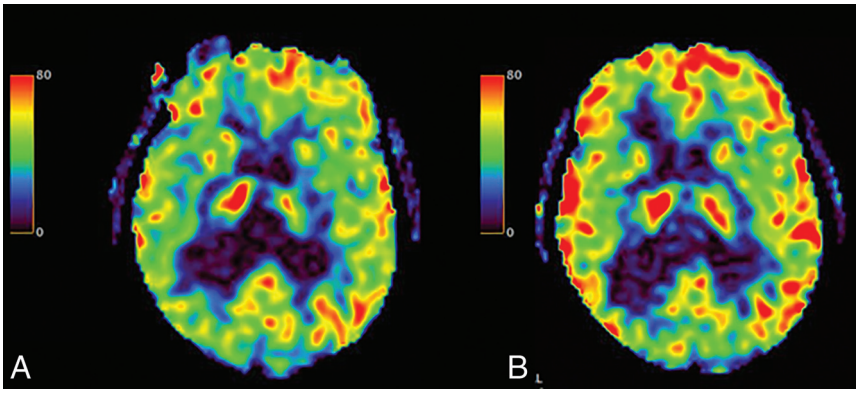

FIG 6. Patient 5 CBF maps. *A*, Baseline CBF map showing cerebral blood flow to be within normal limits. *B*, CBF map before the fifth dose of lecanemab showing increased cerebral perfusion.

AD with an associated inflammatory profile, including elevated oligoclonal bands, possibly triggered by COVID infection. Donepezil, memantine, and desvenlafaxine somewhat improved symptoms. Five days of high-dose methylprednisolone very briefly improved executive function, mood, and alertness. He had 1 microhemorrhage at baseline, but he did not develop ARIA. ASL-MR before the fifth, seventh, and 14th dose monitoring scans for lecanemab did not show improvement in CBF compared with baseline (Fig 5). Clinical history indicated a slight decrease in cognitive function; the prelecanemab MMSE of 22/30 decreased slightly to 21/30 after 9 months of lecanemab therapy. There was no change in mild-moderate volume loss (Supplemental Data). He had no white matter hyperintensities at baseline or on subsequent MRI scans.

CASE 5

A 79-year-old right-handed woman presented with short-term memory loss for 2 years, with mild disorientation and irritability over the past 3 years. Her medical history included Paget disease and hyperlipidemia. Her mother had "AD-like" dementia in her eighties. Cognitive assessments revealed difficulties with short-term memory, working memory, visuoperceptual tasks, phonemic fluency, and naming. Her initial MoCA score was 21/30. ASL-MR and FDG-PET suggested AD, particularly with decreased CBF and metabolism in the temporal lobes (Fig 6, Supplemental Data). Amyloid PET confirmed the AD diagnosis (Supplemental Data). Monitoring MRI scans before the fifth and seventh lecanemab infusions showed improvement in CBF and no ARIA (Fig 6). Cognition was reported as stable by the family. Marked volume loss and mild white matter hyperintensity burden remained stable (Supplemental Data).

CASE 6

A 68-year-old man presented with progressive forgetfulness and personality changes over 5 years, including increased jealousy and irritability. His medical history included hypertension, hyperlipidemia, and type 2 diabetes. Cognitive assessment showed a MoCA score of 14/30, affected by poor vision and low educational attainment; his Clinical Dementia Rating (CDR) should be capitalized (it's a specific validated tool) was 1.0. Family history included a mother with early-onset cognitive impairment and a brother with late-life paranoia.

ASL-MR and FDG-PET were concordant in suggesting AD (Supplemental Data); CSF biomarkers confirmed the diagnosis. The patient received initial treatment with donepezil and olanzapine with some improvement. Lecanemab therapy was then initiated. Monitoring MRI scans before the fifth and seventh infusions showed no ARIA and unchanged CBF (Supplemental Data); the patient's family felt his cognition had remained stable to slightly improved. Mild volume loss and minimal white matter hyperintensity burden remain stable (Supplemental Data).

DISCUSSION

The accumulation of amyloid-β (Aβ) extracellularly in brain parenchyma and along the walls of cerebral blood vessels is a well-described pathologic characteristic of AD.[9] Aβ deposition in the walls and smooth muscle cells of cerebral arteries and arterioles, predominantly Aβ-40, the short form of Aβ, leads to decreased CBF.[9,10] The cases presented in this series highlight how CBF changes on ASL-MR could reflect clearance of Aβ on lecanemab therapy, thereby raising the possibility that ASL-MR could provide an early predictive biomarker of treatment response.

Similar to FDG-PET, longitudinal decline in CBF is associated with cognitive decline,[11-13] likely because of the tight coupling of blood flow, synaptic activity, and glucose metabolism.[14] This series demonstrates that ASL-MR can provide valuable insights into the neurovascular effects of lecanemab within 2–3 months of therapy, with 3 patterns of CBF change demonstrated: continued improvement (Cases 1, 3, 5), immediate increase that reverts to baseline (Case 2), and no improvement (Cases 4 and 6). ASL-MR can thus potentially serve as a noninvasive, cost-effective method for tracking treatment progress before the slowing of cognitive decline can be detected.[9]

In cases of increased CBF, antibody clearance by lecanemab may effectively clear vascular amyloid.[8,15] Preclinical investigations have provided evidence that monoclonal antibody therapies can protect neurons from Aβ-induced apoptosis, leading to neuronal viability and improved brain perfusion.[16] CBF increases may also reflect increased synaptic activity after amyloid clearance and/or vascular changes, such as clearance of fibrinogen/amyloid clotting complexes,[17] further leading to CSF clearance of toxic proteins and improved metabolic activity. Notably, the family of Case 1 reported cognitive improvement, and Case 3 demonstrated objective improvement in the MoCA.

In contrast, some patients did not exhibit substantial changes in CBF despite lecanemab therapy. Cases 4 and 6, for instance, demonstrated persistently low CBF on serial ASL-MR studies. In Case 2, we observed improved CBF before the fifth dose, but this did not persist on the subsequent ASL-MR. An initial increase in CBF may occur due to partial clearance of vascular amyloid.

However, in advanced disease, the extent of amyloid clearance may be insufficient to mitigate disease progression, as other non-amyloid mechanisms may also cause a decline in CBF. These findings highlight varied hemodynamic changes, possibly providing a metric of underlying treatment efficacy. Notably, Cases 2 and 4 had marked atrophy (Supplemental Data), which suggests that patients with more advanced disease may receive less benefit from therapy.[1]

Our series highlights the potential for CBF to serve as a tool for monitoring the neurovascular effects of lecanemab. Unlike structural MRI, which primarily is used to monitor for ARIA-E and ARIA-H, ASL-MR provides both a qualitative and quantitative assessment of cerebral perfusion, which can reflect functional brain changes in response to treatment. The noninvasive nature and relatively low cost of ASL-MR allows it to be easily added to the MRI studies that are already mandated by the FDA during monitoring, further enhancing its suitability for routine clinical use, particularly when repeated measures are necessary. Our series is unique in that serial ASL-MR scans were performed on the same exact MRI scanner, mitigating technical reasons for CBF changes. However, validation of these results in larger cohorts is warranted, and future research can evaluate whether these early changes in CBF can predict true treatment efficacy, as demonstrated by amyloid clearance and slowing of cognitive decline.

This study has several limitations. As a case series, these findings may not be generalizable to the broader population of patients with AD undergoing antiamyloid therapies. Larger cohort studies are needed to validate these results and statistically evaluate the significance of CBF changes across serial ASL-MR. In addition, none of the patients presented had evidence of ARIA; future research will consider the potential effects of ARIA on CBF.

As noted in the Table, several of our patients had vascular comorbidities, which were stable but could potentially influence CBF. We chose not to exclude patients with these vascular comorbidities because patients with AD in real-world settings have high rates of these comorbidities and are being treated with antiamyloid therapies. For example, 1 study reported that almost one-half of their treated patients with AD had hypertension, 24% had diabetes, and more than 70% had hypercholesterolemia.[18] By including such patients in our clinical case series, we show that CBF maps could be informative in these populations as well.

Finally, this study relied on manual ROI analysis, which can be subject to user variability, potential bias, and partial volume effects. However, we chose this form of analysis for easy translation into clinical practice.

Notably, we observed an improvement in cognitive symptoms in cases 1, 3, and 6, although antiamyloid therapies are primarily designed to slow disease progression rather than directly improve clinical symptoms. Further longitudinal clinical follow-up could provide insights into these cognitive improvements. Future work could also determine whether CBF changes reflect changes in cerebral metabolism on FDG-PET or glymphatic clearance by using CSF dynamics or diffusion metrics.

CONCLUSIONS

This case series highlights a potential role for noncontrast ASL-MR to detect changes in CBF in patients with AD receiving lecanemab therapy. The varied response to therapy shown in this case series, although not yet well understood, suggests that CBF changes may provide an opportunity for personalized approaches to monitoring and treatment. ASL-MR offers a promising, noninvasive, and low-cost means to track these changes, which could enhance our understanding and management of AD in clinical practice. Further longitudinal studies are needed to determine whether early CBF improvements can predict better cognitive response to antiamyloid and other upcoming forms of AD therapy.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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