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Amyloid-Related Imaging Abnormalities:
Due Diligence or Overkill?**

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MRI Monitoring of Anti-Alzheimer Therapy Amyloid-Related Imaging Abnormalities: Due Diligence or Overkill?

In a recent article in the *American Journal of Neuroradiology*, Cogswell et al¹ urged radiologists to learn about amyloid-related imaging abnormalities (ARIA) and their MR imaging appearance to be able to diagnose and monitor cerebral changes observed in patients with Alzheimer disease treated with amyloid-targeting monoclonal antibodies. These include aducanumab (marketed as Aduhelm; Biogen), approved by the FDA, and a number of similar treatments currently in clinical trials, eg, donanemab (Eli Lilly), lecanemab (Eisai), gantenerumab (Hoffmann-La Roche), and so forth.

Common to these drugs is the lack of convincing evidence for substantial clinical benefit. They are in no way curative, and multiple trials including thousands of patients have not provided clear, significant evidence of cognitive symptom reduction, let alone reversal. The claim of efficacy for these treatments is largely based on an alleged reduction in cerebral amyloid deposits, which is hypothesized to cause a delay of an inevitable cognitive decline. Surprisingly, therefore, the FDA made an accelerated approval of Aduhelm on June 7, 2021, not only contrary to the vote of its own expert panel but with reference exclusively to what was interpreted as a reduction in cerebral amyloid deposits assessed by serial amyloid PET scans. However, a reduction in PET signals due to treatment is also observed in the white matter, which is known not to have amyloid deposits, but in addition, the effect of therapy-related brain damage, including ARIA, on the PET signal is inexplicably not taken into account.²⁻⁴ These effects are likely either off-target or a result of removing vascular amyloid.

We think that the FDA's approval conflicted with the core of the agency's mission to "protect and promote the public health," because the prevalent adverse effects of these ARIA, also a consideration in the decision of the Centers for Medicare and Medicaid Services (CMS), cannot be ignored. The CMS's restrictive decision not to cover Aduhelm treatments, except for patients enrolled in future CMS-approved trials, is a welcomed initiative.

On that basis, the recommendation of Cogswell et al¹ can be seen as timely care, to the extent that it is becoming increasingly necessary to document the potential damage to patients caused

by these treatments. However, it raises the question of whether MR imaging is the right technique for the purpose. In the published drug trials, the significance of ARIA is minimized and considered to be reversible, as assessed from MR imaging. However, this is not a gospel truth; instead, the ARIA are severe adverse effects of the treatment, demanding a thorough investigation, including their long-term significance for patients.

What is necessary in this connection is to establish the functional impact of the treatment with the FDA/CMS-approved FDG-PET scans, demonstrating regional cortical glucose metabolism as a reliable expression of regional cerebral function. Using MR imaging as the sole indicator of diminishing or disappearing ARIA is, in no way, a guarantee of diminishing or absent brain damage. We, therefore, recommend that the FDA put the approval of Aduhelm on hold, refrain from taking a position on other similar anti-amyloid treatments, and instead require regional brain function assessment by FDG-PET, before and after therapy, of patients who choose to enroll in the trials. Any indication of substantial regional and/or global reduction of brain function in treated patients would provide an indication that the trial should be discontinued.

We welcome radiologists learning about ARIA and how they are best assessed with MR imaging but warn against introducing the method routinely for monitoring of patients with Alzheimer disease on amyloid-targeted immunotherapy, because diminishing or disappearing MR imaging abnormalities may create a false reassurance of the inertness of this kind of 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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