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Aducanumab-Related Amyloid-Related Imaging Abnormalities

Paean or Lament?

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Abstract: When the FDA granted accelerated approval of Biogen's Alzheimer disease drug, aducanumab (marketed as Aduhelm), it deviated from its mission of guaranteeing drug safety and efficacy because the approval was based exclusively on a perceived dose-dependent reduction in brain amyloid deposits and not upon a proven clinical effect. We believe that the amyloid-PET scans, perceived as showing decreasing amyloid deposits, are an expression of increased cerebral cell death due to aducanumab treatment, so that with time one should instead expect a worsening and not an improvement in the treated patients' condition.

Key Words: aducanumab, Aduhelm, Alzheimer disease, amyloid-β, PET

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With the recent accelerated approval of Biogen's Alzheimer disease (AD) drug, aducanumab (marketed as Aduhelm), the FDA deviated from its standard practice of emphasizing safety and efficacy of novel drugs. It granted approval contrary to an almost unanimous vote against by its own advisory panel and solely based on a perceived dose-dependent reduction in brain amyloid deposits as noted on PET scans as evidence for improved cognition. This major decision was made claiming that clinical improvement will become apparent in the future as predicted by this imaging technique.[1]

This approval was unprecedented in the history of the organization. Such a mindset followed the unproven concept of amyloid hypothesis that was introduced 3 decades ago. It stated that AD is due to deposition of the protein amyloid-β ("amyloid") in the brain, and therefore, removing or reducing its load should be anticipated to benefit patients with AD. This concept has been an appealing, but precariously simple-minded and speculative mindset for an immensely complicated disease without any proven mechanism for validating the underlying biochemical process. Furthermore, over the past decade, serious concerns have been raised about the role of radiolabeled compounds to detect and quantify amyloid plaques in the brain.[2] Therefore, without defendable clinical or imaging data as surrogate markers, we believe approval of Biogen's antibody is unjustified. We strongly disagree with the interpretation of the PET scans performed at baseline and following treatment with this drug. Based on our assessment of the published images, reduced tracer uptake in the brain could be due to cell death in the cortex and the white matter in this population, which is very likely to occur following this treatment.

Following the initial report describing amyloid PET imaging results with Pittsburgh compound B (PiB), which appeared 17 years ago,[3] the scientific community became optimistic about its significant impact for diagnosis and monitoring response to treatment in patients with AD. Soon thereafter, based on somewhat questionable postmortem studies of AD patients, amyloid imaging was quickly adopted as the hallmark for the disease. However, follow-up reports appeared showing inconsistent results between the FDG- and amyloid-PET images, and this led to emphasizing the "complementary" and not contradictory roles for these 2 imaging techniques. For example, in AD, amyloid radiotracer uptake is predominantly noted in the frontal lobe, whereas reduced FDG concentration is seen primarily in the temporal-parietal cortices.[4] This observation clearly raises concerns about the interpretation of amyloid images in AD patients. Already a study published in 2006 questioned the rationale behind amyloid-based diagnosis and treatment of AD. In 16 patients, who were examined twice 2 (SD, 0.5) years apart by FDG and PiB, regional cerebral metabolic rate for glucose fell by 20% from the baseline, whereas an expected increase in PiB retention was not substantiated. Furthermore, in the subjects with most advanced disease at baseline and significant cognitive decline during the follow-up, both PiB and FDG uptakes decreased.[5]

Over the past decade, increasingly, the validity of the amyloid hypothesis and its potential impact on managing patients with cognitive impairment has been seriously challenged. Large autopsy studies have noted that amyloid positivity increases from 10% at age 50 years to 40% at age 90 years among subjects with normal cognition, and a meta-analysis of published studies in patients with clinically diagnosed AD has reported significant decrease in amyloid PET positivity with increasing age from 50 to 90 years.[6] The results noted in amyloid scans of normal subjects have been speculated as showing evidence for AD had these subjects lived long enough with the ongoing process. However, the data from the AD group remain unexplained, and the conflicting findings reported over the years question the results from a substantial number of PET amyloid studies. This is in contrast to numerous studies demonstrating validity of findings by FDG PET for accurate diagnosis of AD. Therefore, we believe findings following aducanumab treatment suggest significant cellular death and tissue damage represented by deceased tracer uptake rather than removal of amyloid plaques in patients with AD. Because multiple attempts aiming at reducing amyloid deposits have not resulted in clinical improvement, it seems fair to question the validity of the amyloid hypothesis and the value of amyloid PET imaging as a specific marker for AD.

In a recent article in *JAMA Neurology*, Salloway et al[7] describe certain well-known MRI findings called amyloid-related

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imaging abnormalities (ARIAs) in amyloid-modifying trials. In a secondary analysis of data from the EMERGE and ENGAGE trials of patients with early AD, they report ARIAs in 425 of 1029 patients (41.3%) treated with high-dose (10 mg/kg) aducanumab.[7] One cannot help but wonder if the timing was deliberate. This ARIA report appears 4½ months after and not before the FDA's accelerated approval of aducanumab. The latter was announced on June 7, 2021, claiming a dose-dependent removal of cerebral amyloid deposits and that this will translate to "a reduction in clinical decline."[1]

We are very concerned about the validity of the conclusions reached by the investigator. It is our belief that the PET study findings are due to cerebral cell death and are not related to a decrease in cerebral amyloid. Therefore, aducanumab treatment does not have an impact on declining cognitive function. Frequently observed occurrence of ARIAs is the result of an aggravated brain injury caused by this treatment. Therefore, we advise the FDA to be hesitant to grant accelerated approval of future antibody-based AD therapy, whether directed at amyloid deposits or tau aggregates. Instead, the FDA must require blinded reexamination of the cognitive function of patients who have received placebo and those who have been treated with such antibodies. Very likely, those treated with antibodies will suffer from poor cognition compared with untreated (placebo) subjects.

We believe that future placebo-controlled studies with anti-AD therapy should be followed with FDG PET imaging as a well-established methodology for assessing brain function, instead of amyloid imaging. Obviously, MRI will be of great value for detecting edema and other ARIA changes during ongoing treatment, which "resolve radiographically" in most patients—but in no way preclude permanent cellular damage.

Amyloid-based imaging and treatment have been adopted based on arbitrary and biased views of this concept over the past 2 decades, and therefore, it has no role in assessing patients with either mild cognitive impairment or dementias. The validity of antiamyloid antibodies for treating early or advanced AD is also very questionable. Reduced uptake of amyloid tracer following treatment with antiamyloid drugs is primarily due to significant damage to the brain as has been demonstrated in a large segment of patients with this disease. Amyloid-related imaging abnormalities are due to significant swelling and bleeding and possibly other injuries that follow this type of treatment and provide the best explanation for decreased uptake of amyloid tracers. Furthermore, decreased uptake of such tracers is primarily noted in the white matter, which lacks amyloid plaques. On the whole, approval of Biogen's drug, aducanumab, with reference to reduced amyloid plaque after treatment is most likely based on misinterpretation and thus unjustified.

REFERENCES

1. Cavazzoni P, FDA Center for Drug Evaluation and Research. FDA's Decision to Approve New Treatment for Alzheimer's Disease. US Food and Drug Administration. Available at: https://www.fda.gov/drugs/news-events-human-drugs/fdas-decision-approve-new-treatment-alzheimers-disease. Accessed November 29, 2021.
2. Alavi A, Barrio JR, Werner TJ, et al. Suboptimal validity of amyloid imaging-based diagnosis and management of Alzheimer's disease: why it is time to abandon the approach. *Eur J Nucl Med Mol Imaging*. 2020;47:225–230.
3. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh compound-B. *Ann Neurol*. 2004;55:306–319.
4. Cohen AD, Klunk WE. Early detection of Alzheimer's disease using PiB and FDG PET. *Neurobiol Dis*. 2014;72:117–122.
5. Engler H, Forsberg A, Almkvist O, et al. Two-year follow-up of amyloid deposition in patients with Alzheimer's disease. *Brain*. 2006;129:2856–2866.
6. Høilund-Carlsen PF, Barrio JR, Gjedde A, et al. Circular inference in dementia diagnostics. *J Alzheimers Dis*. 2018;63:69–73.
7. Salloway S, Chalkias S, Barkhof F, et al. Amyloid-related imaging abnormalities in 2 phase 3 studies evaluating aducanumab in patients with early Alzheimer disease. *JAMA Neurol*. 2022;79:13–21.