Journal of Alzheimer's Disease 82 (2021) 461–462
DOI 10.3233/JAD-210383
IOS Press

Editorial

New IDEAS Amyloid Imaging 2021 Study: Running in Place with Ineffective Anti-Amyloid Treatments for Alzheimer's Disease Patients

Jorge R. Barrio[a,*], Peter Whitehouse[b,c], Abass Alavi[d] and Poul F. Høilund-Carlsen[e,f,*]
[a]*Department of Molecular and Medical Pharmacology, David Geffen UCLA School of Medicine, Los Angeles, CA, USA*
[b]*Case Western Reserve University, Cleveland, OH, USA*
[c]*University of Toronto, Toronto, ON, Canada*
[d]*Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA, USA*
[e]*Department of Nuclear Medicine, Odense University Hospital, Odense, Denmark*
[f]*Department of Clinical Research, University of Southern Denmark, Odense, Denmark*

Accepted 3 May 2021
Pre-press 20 May 2021

Keywords: IDEAS study, Alzheimer's disease, amyloid imaging, clinical usefulness

With the same perseverance observed with the failed anti-amyloid treatments for Alzheimer's disease (AD), the Alzheimer's Association and the American College of Radiology have now launched a new IDEAS study: "Imaging Dementia — Evidence for Amyloid Scanning" early 2021 and are now accepting applications from imaging facilities interested in participating (https://www.ideas-study.org/Getting-Started). This new call is supported by questionable lines of evidence suggesting that the original IDEAS study launched in 2016 provided the strongest data to date supporting the clinical utility of amyloid imaging (positron emission tomography (PET) Aβ imaging).

In the background is the 2013 Centers for Medicare & Medicaid Services (CMS) decision denying reimbursement of PET Aβ imaging because the evidence obtained in phase III clinical trials was 'insufficient to conclude that the use of PET amyloid-beta (Aβ) imaging is reasonable and necessary for the diagnosis or treatment of illness' [1]. Most recently, reported clinical evidence from the first IDEAS study has indicated that no changes in patient outcomes or even

*Correspondence to: Jorge R. Barrio, PhD, David Geffen School of Medicine at UCLA, Department of Molecular and Medical Pharmacology, CHS B2-086A, 694817, 10833 Le Conte Avenue, Los Angeles, CA 90095-6948, USA. E-mail: jbarrio@mednet.ucla.edu; Poul F. Høilund-Carlsen, MD, DMSc, Prof (Hon), Department of Nuclear Medicine, Odense University Hospital, 29 Sdr. Boulevard, 5000 Odense C, Denmark. Tel.:+45 2521 5445; E-mail: pfhc@rsyd.dk; ORCID ID: 0000-0001-7420-2367.

ISSN 1387-2877/$35.00

hospitalizations have been achieved with the use of PET Aβ imaging in these patients [2].

This PET Aβ imaging initiative invites speculation as to why it is pursued, beyond the incentive of the CMS financial support, despite severe limitations. This is a problematic approach, when all available experience and scientific evidence supported by multiple clinical trials have repeatedly shown that neither anti-amyloid treatments nor PET Aβ imaging can provide useful solutions to improve diagnosis and treatment of patients with known or suspected AD [3].

Granted, AD is a difficult therapeutic target. In the process of neurodegeneration, the brain of AD patients loses tens of billion neurons in a concerted and progressive fashion, following specific neuronal pathways. Obviously, treatment in advanced stages has severe limitations if changing course of the disease is the purpose. It is logically anticipated that successful treatments are best achieved with preventive measures or with treatments at the earliest possible stages of the disease, when neurodegeneration is minimum. Evidence has shown so far that removing amyloid plaques from the brain of AD patients is akin to removing deployed airbags from the scene of a car accident. No substantial positive effects are observed.

Similarly, this new IDEAS initiative has very low likelihood for success, based on the lack of diagnostic value of PET Aβ imaging or resulting changes in patient outcomes. As previously summarized, the suboptimal specificity of amyloid imaging, lack of correlation between amyloid deposits and dysfunctional neuronal pathways, insufficient distinction between early and late onset AD, and minimal or non-existent cost-effectiveness or insurance reimbursement of PET Aβ imaging, all question scientific initiatives hinged on the amyloid hypothesis [4]. Add to this that a multidisciplinary research team at the Scripps Research Institute, La Jolla, CA, recently found that experimental antibody drugs for AD and Parkinson's disease may trigger in mice with brain grafts of human induced pluripotent stem cell-derived microglia the NLRP3 inflammasome and lead to cell death [5]. This may be indicative of the results of these anti-amyloid treatments with patients: Patients do not improve cognitively, and many get worse and even die earlier.

Moreover, *post hoc* analysis of already published negative antibody treatment trials will not do the job and convince of the beneficial effects of anti-Aβ monoclonal antibody treatment of AD patients as recently pointed out by Alexander et al. in *JAMA* [6]. These procedures are allowed exclusively to generate ideas for new prospective studies and cannot serve as evidence.

Thus, it is time to focus instead on scientific initiatives driven by targetable basic biology that may participate in the genesis of the disease or act as drivers of various molecular and cellular pathways of AD pathogenesis. These research initiatives should involve independent, unbiased investigators from academic, national, and commercial institutions that support such forthcoming objective research. Only in this way we can ensure that history does not repeat itself and prevent the continued wasting of resources, while the buck is passed on to patients and society with the false pretense that the IDEAS, and related anti-amyloid therapeutic initiatives, are a gift to society and to patients with AD.

DISCLOSURE STATEMENT

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/21-0383r1).

REFERENCES

[1] Centers for Medicare and Medicaid Services (2020) Decision Memo for Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease (CAG-00431N). CMS.gov https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=265. Posted 8 May 2020. Accessed 25 February 2021.

[2] Marchione M (2020) Medicare Coverage for Alzheimer Brain Scans in Question. *ABC News Network*, https://abcnews.go.com/US/wireStory/medicare-coverage-alzheimer-brain-scans-question-72075057. Posted 30 July 2020. Accessed 25 February 2021.

[3] Kepe V, Moghbel MC, Långström B, Zaidi H, Vinters HV, Huang SC, Satyamurthy N, Doudet D, Mishani E, Cohen RM, Høilund-Carlsen PF, Alavi A, Barrio JR (2013) Amyloid-β positron emission tomography imaging probes: A critical review. *J Alzheimers Dis* **36**, 613-631.

[4] Høilund-Carlsen PF, Barrio J, Gjedde A, Werner TJ, Alavi A (2018) Circular inference in dementia diagnostics. *J Alzheimers Dis* **63**, 69-73.

[5] Trudler D, Nazor KL, Eisele YS, Eisele YS, Grabauskas T, Dolatabadi N, Parker J, Sultan A, Zhong Z, Goodwin MS, Levites Y, Golde TE, Kelly JW, Sierks MR, Schork NJ, Karin M, Ambasudhan R, Lipton SA (2021). Soluble α-synuclein–antibody complexes activate the NLRP3 inflammasome in hiPSC-derived microglia. *Proc Natl Acad Sci U S A* **118**, e2025847118.

[6] Alexander GC, Emerson S, Kelleheim AS (2021) Evaluation of aducanumab for Alzheimer disease: Scientific evidence and regulatory review involving efficacy, safety, and futility. *JAMA* **325**, 1717-1718.