Inflammopharmacology (2023) 31:1027–1028
https://doi.org/10.1007/s10787-023-01172-6

Inflammopharmacology

EDITORIAL

The amyloid hypothesis revisited: are monoclonal antibodies truly effective?

Joel Ross[1] · Izhar Hasan[1]

Received: 2 December 2022 / Accepted: 10 January 2023 / Published online: 30 March 2023

The amyloid hypothesis first proposed by Hardy was based upon a rare genetic mutation in early onset AD patients (Hardy and Higgins 1992). The great majority of AD patients do not carry such genetic mutations. Attempts to lower amyloid using monoclonal antibodies, BACE and gamma secretase inhibitors have not yielded clinically significant benefits in AD patients.

The amyloid hypothesis is flawed in many respects:

1. Amyloid deposits in AD brains are frequently found in the brains of cognitively normal older adults (Reiman et al. 2009)
2. Postmortem analysis reveals presence of acetylated tau as well as phosphorylated tau before amyloid deposits are noted in Alzheimer's Disease (Lucke-Wold et al. 2017)
3. Deposition of amyloid is likely a "secondary" reaction to early neuropathological events such as neuroinflammation/post translationally modified tau protein (Rischel et al. 2022)

Despite the myriad of failed AD treatments aimed at lowering brain levels of amyloid, one drug has been conditionally approved by the US FDA, the Biogen monoclonal antibody Aducanumab (FDA 2022).

This approval came after the entire advisory board recommended NOT to approve the drug. In the latest publication from Biogen and Eisai,

Lecanemab, a monoclonal antibody, reports the only primary clinical outcome (utilizing the CDR Sum of Boxes) of a reduction of 0.45 points (van Dyck 2022). In clinical practice such a reduction has no clinically meaningful benefit despite the statistically significant outcome reported ($(p < 0.001)$. All secondary outcome measures have no clinically relevant benefit and should not be interpreted as a clinically useful "positive outcome" of the study.

Furthermore, the reported MRI abnormalities of cerebral edema and effusions occurring in 12.6% of patients is quite significant as neurological sequelae can be seen with recurrent infusions with any amyloid lowering monoclonal antibody. Lastly, as in all clinical studies there is an extensive number of exclusionary criteria which would put at unknown additional risk those who have such criteria if given Lecanemab.

Funding The authors have not disclosed any funding.

Data availability Enquiries about data availability should be directed to the authors.

Declaration

Competing interests The authors have not disclosed any competing interests.

References

FDA 2022: https://www.fda.gov/drugs/postmarket-drug-safety- information-patients-and- providers/aducanumab-marketed-aduhelm- information

Hardy JA, Higgins GA (1992) Alzheimer's disease: the amyloid cascade hypothesis. Science 256(5054):184–185

Lucke-Wold B, Ross J et al (2017) Role of tau acetylation in Alzheimer's disease and chronic traumatic encephalopathy: the way forward for successful treatment. J Neurol Neurosurg. 4(2):140

✉ Izhar Hasan
jrossmd@gmail.com

[1] Rutgers University School of Medicine, Piscataway, NJ, USA

Reiman E, Chen K et al (2009) Fibrillar amyloid-β burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. Proc Nat Acad Sci. 106(16):6820–6825

Rischel EB, Geli M et al (2022) In Alzheimer's disease, amyloid beta accumulation is a protective mechanism that ultimately fails. Alzheimer Dement. https://doi.org/10.1002/alz.12701

van Dyck CH et al (2022) Lecanemab in early Alzheimer's disease. N Engl J Med. https://doi.org/10.1056/NEJMoa2212948