Statement on Off-Label Use of Aducanumab for Treatment of Cerebral Amyloid Angiopathy

The anti-amyloid β monoclonal antibody aducanumab was approved 7 June 2021 by the US Food and Drug Administration (FDA) for treatment of Alzheimer's Disease (AD).[1] Approval was provided under FDA's accelerated approval process for drugs that treat serious conditions and fill an unmet need and was based on the surrogate endpoint of reduction of amyloid β plaques in the brain.

The FDA approved aducanumab specifically for AD and noted in its prescribing information that "the safety of ADUHELM in patients with any pre-treatment localized superficial siderosis, 10 or more brain microhemorrhages, and/or with a brain hemorrhage greater than 1 cm within one year of treatment initiation has not been established."[2] US physicians, nevertheless, will be able to prescribe aducanumab off-label for the related condition of cerebral amyloid angiopathy (CAA) and may be tempted to do so. CAA, like AD, is thought to be triggered by accumulation of amyloid β deposits in the brain, in CAA occurring in cerebral small arteries, arterioles, and capillaries with consequent intracerebral haemorrhage and vascular brain injury. As leaders of the International CAA Association and clinicians and investigators in the CAA field, we believe there are substantial uncertainties and concerns about both the safety and efficacy of aducanumab for patients diagnosed with CAA.[3] We therefore believe aducanumab should not be used for the purpose of treating CAA outside the context of a research trial.

From a clinical efficacy standpoint, anti-amyloid β immunotherapy, though a rational approach to CAA that we believe should continue to be explored, has not been shown to provide benefit. Cerebrovascular amyloid β deposits appear relatively refractory to antibody-mediated clearance and may be worsened by mobilization of solubilized plaque amyloid into the perivascular spaces where CAA occurs.[4] The one immunotherapy trial performed in CAA patients using the anti-amyloid β antibody ponezumab found a trend towards reduced rather than enhanced cerebrovascular reactivity following three monthly infusions.[5] There is thus no evidence to date of beneficial CAA disease modification for anti-amyloid β immunotherapy.

The concern from a safety standpoint is the potential of CAA to promote the amyloid-related imaging abnormalities (ARIA) that have emerged as the major adverse events in AD trials of aducanumab and other antibodies. Presence of advanced CAA, inferred by markers such as cerebral microbleeds or the *APOE*ε4* allele, appears to increase the likelihood of ARIA.[4] CAA is postulated to promote ARIA by compromising perivascular amyloid clearance pathways and by providing a target for direct antibody-mediated attack on amyloid β -laden vessels. The incidence of ARIA in aducanumab-treated CAA patients would thus be predicted to exceed the substantial rates observed in the recent AD trials (ARIA-E edema in 35% of AD patients receiving the full 10 mg/kg aducanumab dose, ARIA-H microhaemorrhages and superficial siderosis in 21%).[2]

In the absence of evidence supporting efficacy and the existing evidence suggesting increased ARIA risk, aducanumab should not currently be considered a treatment option for disease

modification of sporadic or hereditary CAA. We strongly discourage its off-label use for these disorders outside of any future clinical trial.

REFERENCES

1. FDA Grants Accelerated Approval for Alzheimer's Drug. 2021. https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug (accessed June 17, 2021 2021).
2. Prescribing Information — US Food and Drug Administration — ADUHELM. 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf (accessed June 17, 2021 2021).
3. Greenberg SM, Charidimou A. Diagnosis of Cerebral Amyloid Angiopathy: Evolution of the Boston Criteria. *Stroke* 2018; **49**(2): 491-7.
4. Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease - one peptide, two pathways. *Nat Rev Neurol* 2020; **16**(1): 30-42.
5. Leurent C, Goodman JA, Zhang Y, et al. Immunotherapy with ponezumab for probable cerebral amyloid angiopathy. *Ann Clin Transl Neurol* 2019; **6**(4): 795-806.