

## Open the Blood-Brain Barrier for Aducanumab by Focused Ultrasound

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### Key highlights:

- Aducanumab is a human anti-amyloid monoclonal antibody indicated for the treatment of Alzheimer's disease (AD).
- The blood-brain barrier (BBB) prevents most biologic drugs from effective delivery to the brain.
- Low-intensity focused ultrasound (FUS) can temporarily and reversibly open the BBB in targeted brain regions precisely.
- A proof-of-concept clinical trial demonstrated FUS BBB opening shortly after aducanumab infusion which enhanced amyloid clearance in sonicated brain regions in patients with AD.

A proof-of-concept clinical trial, led by Ali R. Rezai, M.D. of the Western Virginia University Rockefeller Neuroscience Institute, demonstrated the potential of blood-brain barrier opening (BBBO) by magnetic resonance imaging (MRI) – guided focused ultrasound (FUS) (MRgFUS) to facilitate aducanumab-mediated clearance of amyloid in patients with Alzheimer's disease. This exciting study was published in the *New England Journal of Medicine* early this year (Rezai, D'Haese et al. 2024).

Aducanumab is one of two US FDA-approved human anti-amyloid- $\beta$  (A $\beta$ ) immunoglobulin gamma 1 monoclonal antibodies for the treatment of AD. The soluble A $\beta$  and misfolded A $\beta$  oligomers are neurotoxic. Along with tau, A $\beta$  drives the neurodegenerative process of AD. Because the blood-brain barrier (BBB) excludes more than 98% of small-molecule drugs and nearly 100% of large-molecule biological drugs from entering the brain (Pardridge 2005), a higher injection dose of aducanumab (gradual titration up to 10 mg/kg) is required for BBB penetration. Intravenous aducanumab has been shown to reduce brain amyloid burden measured in standardized uptake value ratio (SUVR) and centioid (CL) units by positron emission tomography (PET) in a dose-dependent manner (Budd Haeberlein, Aisen et al. 2022). The most common adverse event in amyloid-related imaging was edema (ARIA-E) which was also dose-dependent (Budd Haeberlein, Aisen et al. 2022). The linear relationship between the ability to clean amyloid plaques and the emergence of ARIA-E suggests drug-induced BBB disruption as the main BBB avoidance strategy for aducanumab to enter brain tissues (Pardridge 2020).

Recent technical progress has made it possible to generate ultrasound beams that pass through the skull and is focused on a small target area of the brain. High-intensity FUS can be

used non-invasively for precise thermoablation of brain tissues key in circuits underlying neuropsychiatric disorders, such as essential tremors, tremor-dominant Parkinson's disease, obsessive-compulsive disorder, etc. Reversible BBBO can be achieved with low-intensity MRgFUS without significant temperature rise. During MRgFUS BBBO, the intravenous-injected microbubbles undergo oscillatory compression and expansion when passing through vessels under the FUS field. The cavitation mechanical forces to the capillary walls result in transient damage to the tight junctions between endothelial cells. In addition, paracellular transport is also enhanced. Other biological effects of FUS include neuromodulation, hyperthermia, targeted uncaging of nanodroplets for drug delivery, and histotripsy (for review, please refer to (Meng, Hynynen and Lipsman 2021)).

In a preliminary study, Rezai AR, et al. have demonstrated the cognitive and neurological safety of reversible and repeated MRgFUS BBBO (Rezai, Ranjan et al. 2023). Ten subjects with mild AD received three BBBO treatments with an inter-treatment interval of 2 weeks and were followed for 0.5 to 1 year. BBBO was observed immediately after FUS, and closure was observed within 24 to 48 hours. An average of 5% A $\beta$  reduction measured in Standard Uptake Values Ratio (SUVR) or a corresponding 14% reduction in the Centiloid scale by PET imaging was observed in the FUS-targeted regions.

Then in the proof-of-concept clinical trial combining BBBO and aducanumab, MRgFUS BBBO was applied two hours after each of the six doses of monthly intravenous aducanumab in three patients with probable mild cognitive impairment or probable mild Alzheimer's disease (Rezai, D'Haese et al. 2024). The target BBBO regions were restricted to those with a high level A $\beta$  in one hemisphere, and the homologous regions in the contralateral hemisphere served as the control in measuring the extent of amyloid clearance. The total brain volumes of BBBO were up to 10 ml in the right frontal lobe of participant 1, 20 ml in the left frontal and parietal lobes of participant 2, and 40 ml in the left frontal, parietal, and temporal lobes, and the hippocampus in participant 3. The dose of aducanumab was escalated up gradually from 1 mg/kg for the first two doses to 6 mg/kg for the last two doses. An average reduction of 32% in SUVR was observed in BBBO regions after 26 weeks (from PET at baseline to PET after the 6<sup>th</sup> combination treatment). The difference between amyloid plaque reduction between homologous brain regions with and without sonication was on average 53% centiloids. During the 6-month combination treatment, no serious adverse events were observed. Cognitive worsening without compromise of activities of daily life was noted in one participant. Although ARIA-E was not observed, this clinical trial excluded carriers of the apolipoprotein E  $\epsilon$ 4 genotype ( $\epsilon$ 4/ $\epsilon$ 4 and  $\epsilon$ 3/ $\epsilon$ 4) which has been a known risk factor for ARIA.

The clinical trial demonstrated FUS BBBO techniques may facilitate the development of biologic drugs for treating AD and other CNS disorders (Pardridge 2020). However, animal studies have shown BBBO alone may reduce A $\beta$ , enhance neural plasticity and improve cognitive function (Burgess, Dubey et al. 2014). A recent study even found that scanning-mode ultrasound without BBBO by microbubble injection improved memory deficits in the APP23 mouse model of AD (Leinenga, To et al. 2024). More clinical trials are needed to validate the cognitive benefits in addition to A $\beta$  clearance and the long-term safety of combining FUS BBBO and anti-amyloid antibody treatments.

### For further reading:

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