Donanemab removes Alzheimer's plaques: what is special about its target?

A phase 2 clinical trial of donanemab, a humanised immunoglobulin G1 monoclonal antibody that specifically targets N-terminally truncated pyroglutamate-modified amyloid β ($Aβ_{pE}$), showed a substantial reduction in Alzheimer's disease-associated cerebral amyloid-plaque load, measured by amyloid positron emission tomography (PET), in the intervention group compared with the placebo group.[1] Following the 76 week trial period, donanemab reduced amyloid PET binding by 84·1 centiloids compared with an increase of 0·93 centiloids in the placebo group (from a mean baseline of 108 centiloids in the intervention group *vs* 101 centiloids in the placebo group). In fact, by week 76, approximately two thirds of the participants receiving donanemab were amyloid-PET negative.

Although there have been many trials of antibodies against amyloid in Alzheimer's disease, donanemab appears to have produced a remarkable amount of plaque clearance. The anti-amyloid β (Aβ) antibodies that have been trialled thus far have been heterogenous, targeting different domains and aggregation states of the Aβ peptide. Some are selective for plaques, while others are thought to target monomeric, oligomeric, or fibrillar forms of Aβ. There is considerable heterogeneity in the composition and morphology of Aβ in the brain, and some of the antibodies also bind to normal Aβ. One important aspect of donanemab is that it targets $Aβ_{pE}$, a form of Aβ detectable solely within cerebral Aβ plaques, and not found within biofluids (cerebrospinal fluid or plasma) or in cell media from neurons derived from human stem cells, suggesting it is plaque specific.[2] Understanding where and how $Aβ_{pE}$ formation occurs is important for establishing its role in pathogenesis, and its promise as a target for Alzheimer's disease treatment. What is it about $Aβ_{pE}$ that makes it such an effective immunotherapy target?

Aβ peptides are widely known to vary at their C termini. However, *in-vivo* analyses and *in-vitro* analyses have revealed a heterogeneity in the N terminus of the peptide in Alzheimer's disease. Indeed, several N-terminally truncated and modified species of Aβ have been observed in brains of patients with Alzheimer's disease, with Harigaya and colleagues[3] showing that although Aβ ending at amino acid 40 is the dominant form of Aβ in cerebral blood vessels and Aβ ending at amino acid 42 is the dominant form in parenchymal plaques, only a small proportion is made up by $Aβ_{1–40}$ and $Aβ_{1–42}$. This finding suggests that most Aβ ending at amino acids 40 and 42 present in the brains of patients with Alzheimer's disease is truncated or modified. Interestingly, *in-vitro* analysis has shown that N-terminally truncated Aβ species have a greater propensity to aggregate than their full-length counterparts.[4]

$Aβ_{pE}$ is of interest as it has been shown to be one of the dominant forms of Aβ present in the hippocampi and cortices of patients with Alzheimer's disease. However, arguably of most importance is that $Aβ_{pE}$ is specifically only found within cerebral Aβ plaques.[2] *In-vitro* analysis has revealed that $Aβ_{pE3}$ shows an increased rate of aggregation up to 250 times that of full-length Aβ, irrespective of its C terminus.[5] The N-terminal pyroglutamate structure is known to be resistant to degradation by peptidases, thus increasing peptide stability.[6] Furthermore, $Aβ_{pE}$ has been found in a range of brain regions in greater concentrations than full-length Aβ, suggesting that it is deposited earlier in the disease process.[6] Finally, Güntert and colleagues[7] observed a correlation between the presence of $Aβ_{pE3}$ and disease severity, supporting early transgenic-mouse studies.

Pyroglutamate, or pyrrolidone carboxylate, is a cyclic amino acid typically found at the N terminus of some proteins and peptides. $Aβ_{pE}$ is formed by the cyclisation of either glutamine or glutamate by the enzyme glutaminyl cyclase at amino acid positions 3 or 11 of Aβ, following truncation by N-terminal proteases.[8]

It is clear that $Aβ_{pE}$ is a pathology-specific form of Aβ that is not produced by neurons, but is formed within plaques. Targeting this particular form of Aβ with an antibody such as donanemab should not affect normal Aβ, which might reduce the risk of amyloid-related imaging abnormalities (ARIA). In particular, ARIA with oedema and effusions (ARIA-E) is a prominent side-effect associated with amyloid immunotherapies.[9] Nonetheless, in the donanemab study, as with other Aβ immunotherapy trials, ARIA-E had a significantly greater rate of occurrence among participants in the donanemab group (26·7%) than those in the placebo

group (0·8%).[1] Of patients who had ARIA-E, only 22% (ie, 6·1% of the whole donanemab group) were symptomatic. Arguably, the occurrence of ARIA-E and symptomatic ARIA is low, given the extent of cerebral amyloid clearance, and is lower than in some other trials.[10]

In the donanemab study, cognitive decline slowed by a third, meeting the primary endpoint. Finally, the treatment appeared to reduce tangles and worked best at low tangle loads.[1] In light of this finding, further clinical trials on donanemab and developing additional drug therapies that target $A\beta_{pE}$ might be important to identify an effective drug against Alzheimer's disease.

NCF has served as a consultant, on advisory boards, or on a data-monitoring committee for Roche, Biogen, and Ionis. HZ has served on scientific-advisory boards for Eisai, Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics, Nervgen, AZTherapies, and CogRx, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, and Biogen, and is a cofounder of Brain Biomarker Solutions in Gothenburg AB (also known as BBS), which is part of the GU Ventures Incubator Programme. DOTA and AJH declare no competing interests.

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