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# Updates on pharmacological treatment for Alzheimer's disease: response to Letter to the Editors

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## To the Editors

The past two years have brought major advances to the treatment landscape of Alzheimer's disease (AD). Once a disease with mediocre symptomatic treatment, AD will soon have three disease-modifying therapies available (aducanumab, lecanemab, and donanemab). This journal recently published my review of the pharmacological advances in AD treatment [1]. In their Letter to The Editors, Gaggero et al. noted that my review did not discuss treatment of cerebral amyloid angiopathy (CAA) despite its high concurrence with AD [2]. Herein, I discuss evidence regarding the risk and potential benefit of treating CAA with monoclonal antibodies directed against amyloid- $\beta$  (A $\beta$ ).

Amyloid-related imaging abnormality (ARIA) is a well-documented adverse effect of anti-amyloid therapies that manifests with edema (ARIA-E) and/or haemorrhage (ARIA-H). ARIA is usually asymptomatic, but can be life-threatening and has been observed in virtually all trials of monoclonal antibodies directed against A $\beta$ . Numerous trials of anti-amyloid therapies have failed to demonstrate significant efficacy, but have taught us that certain patient characteristics, such as APOE $\epsilon$ 4 allele homozygosity, as well as imaging features suggestive of CAA, increase one's risk of developing ARIA.

CLARITY AD was the first non-disputed positive phase III clinical trial of an anti-amyloid monoclonal antibody to treat AD [3]. To minimise the occurrence of ARIA, CLARITY AD excluded individuals with any of the following: > 4 microhaemorrhages ( $\leq$  10 mm at greatest diameter);  $\geq$  1 macrohaemorrhage (> 10 mm at greatest diameter); or superficial siderosis [3]. The donanemab

trial also adopted these exclusion criteria [4]. Despite effectively excluding individuals with known CAA, ARIA-H still occurred in 17.3% of patients in the treatment arm of CLARITY AD [3]. Fortunately, only six individuals receiving lecanemab were symptomatic.

Despite the demonstrable benefit of anti-amyloid therapies in AD, there is no compelling evidence supporting their use in CAA due to the lack of positive primary outcomes in phase III clinical trials. Even theoretical efficacy is lacking, because potential study enrollees with imaging features of CAA were excluded from the only positive AD clinical trials due to their increased risk of developing ARIA-H. Cummings et al. recently published appropriate use guidelines for lecanemab, and recommended adopting the same inclusion/exclusion criteria of CLARITY AD when deciding which patients should be offered lecanemab [5].

Monoclonal antibodies directed against A $\beta$  may be an effective therapeutic approach for CAA, but require additional study. A $\beta$ 40 is the primary amyloid isoform of CAA as opposed to A $\beta$ 42 in AD. Ponezumab is a monoclonal antibody directed against A $\beta$ 40, and a recent phase II clinical trial demonstrated safety and tolerability but did not meet efficacy criteria [6]. Like other amyloidoses (e.g. transthyretin amyloidosis), alternatives to monoclonal antibodies may be more effective for treating CAA.

In conclusion, there is much work to be done before a CAA treatment is ready for the clinic.

## Article information

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