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The impending era of beta-amyloid therapy: Clinical and research considerations for treating vascular contributions to neurodegeneration

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The dawning of a new era of disease-modifying therapy for Alzheimer's disease (AD) may be imminent. For the first time, positive results from more than one trial of beta-amyloid lowering therapy have been published. Increasingly, the data suggest that removing beta-amyloid plaques from the brain may reduce the rate of functional cognitive decline by approximately one quarter. If confirmed, this will revolutionize care for dementia. This potential breakthrough will impose new obligations for the assessment of vascular contributions to cognitive decline and dementia (VCID), new potential dangers, and new opportunities to invigorate clinical trials for VCID.

The controversy surrounding the United States (U.S.) Food and Drug Administration (FDA) approval and marketing of Biogen's aducanumab–against the recommendations of their expert advisory panel, and marked by deviations from the FDA's own protocols according to its internal review and a congressional investigation—obscured the remarkable fact that for the first time a drug had been proven in clinical trials to effectively remove senile plaques in living people. Aducanumab was granted accelerated approval by the FDA based on its ability to reduce amyloid plaque load, a proposed surrogate treatment marker. However, critics pointed out that the evidence linking beta-amyloid removal to better cognitive function was weak. Despite the FDA approval, U.S. Medicare declined to cover costs of the drug in routine practice. The European Union declined to approve it at all. With little hope of a market developing for aducanumab, Biogen stopped promoting it. A previous editorial in *Cerebral Circulation-Cognition and Behavior* urged caution in accepting Biogen's interpretation of the results and pointed out implications for VCID research [1].

More recently, lecanemab has been reported to reduce decline in the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) by 27% in a phase 3 trial [2], and donanemab has been reported to reduce decline in Integrated Alzheimer's Disease Rating Scale by 32% in a phase 2 trial [3]. By comparison, aducanumab reduced decline in CDR-SB by 22% in the EMERGE trial but did not reduce decline in the ENGAGE trial [4]. On January 6, the FDA announced approval for lecanemab under the same accelerated approval process that was used for aducanumab. Whether lecanemab will gain traction in the marketplace remains to be seen. The E.U. has not made a decision yet on lecanemab, and U.S. Medicare has not evaluated it yet for coverage for seniors. However, given the increasing evidence of a statistically significant, but modest, effect on slowing cognitive decline, it seems more and more likely that monoclonal antibody treatments will be entering clinical practice soon.

If use of anti-beta-amyloid monoclonal antibody therapy becomes widespread, it will obligate clinicians to accurately diagnose cerebral amyloid angiopathy (CAA), a common cause of VCID, to reduce risk for amyloid-related imaging abnormalities-edema (ARIA-E) and -hemorrhage (ARIA-H). CAA appears to be the main risk factor for ARIA [5]. Although most ARIA events are silent, detected on imaging only, and can be managed by dose reduction with slow resumption starting at a lower dose, a few percent of events are symptomatic and can lead to serious injury or death [6]. The lower reported incidence of ARIA in trials of lecanemab relative to aducanumab (Table 1) raised hopes that this may be less of a concern for lecanemab. This hope was undermined, however, by a recent report of fatal intracerebral hemorrhage and CAA-related vasculitis in a patient treated with intravenous thrombolysis for an ischemic stroke while receiving lecanemab in open-label extension [7]. Another patient in the open-label extension phase had a cerebral hemorrhage and died while taking anticoagulation for atrial fibrillation [8]. We suggest caution when considering the use of lecanemab in patients taking anticoagulants, pending more data, consensus recommendations, and labeling by drug regulatory authorities. We recommend that post-marketing studies and registries be created to learn more about the risk for adverse events on these drugs.

Diagnosing CAA requires clinicians, including VCID specialists and radiologists, to accurately recognize microbleeds and cortical superficial siderosis. Clinicians will need to increase their familiarity with CAA diagnostic criteria, including the recently published Boston criteria version 2.0 [9]. All of the anti-abeta monoclonal trials excluded patients based on hallmarks of CAA such as multiple lobar microbleeds or

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Table 1
Exclusion criteria and outcomes related to amyloid-related imaging abnormalities (ARIA) in recent phase 2 and 3 trials of beta-amyloid immunotherapies for Alzheimer's disease.

Trial	Antibody	Hemorrhage exclusion	Cortical superficial siderosis exclusion	ARIA-H		ARIA-E	
				Total**	Symptomatic	Total**	Symptomatic
EMERGE[4]	aducanumab*	>4 microbleeds, or one or more macrohemorrhages (>10 mm diameter)	any	20.0%/ 13.5%	†	34.7%	†
ENGAGE [4]	aducanumab*	>4 microbleeds, or one or more macrohemorrhages (>10 mm diameter)	any	18.8%/ 16.1%	†	35.9%	†
CLARITY AD [2]	Lecanemab	>4 microbleeds, or one or more macrohemorrhages (>10 mm diameter)	any	17.3%	0.7%††	12.6%	2.8%
TRAILBLAZER-ALZ [3]	donanemab	>4 microbleeds	any	30.5%	0%	27.5%	6.1%

Legend: ARIA-H, amyloid-related imaging abnormalities – hemorrhage; ARIA-E, amyloid-related imaging abnormalities – edema.
* Proportions are for the high dose arm.
** Proportion with either new microbleeds or cortical superficial siderosis; except for EMERGE and ENGAGE, where they were reported separately and are displayed as percent with new microbleeds / percent with new cortical superficial siderosis.
† Reported overall, not stratified by ARIA-H and ARIA-E. In EMERGE, 20% reported symptoms with an ARIA-H or ARIA-E episode, and in ENGAGE 29% reported symptoms with an ARIA-H or ARIA-E episode. No serious adverse events due to hemorrhages were reported.
†† Dizziness was reported to be the most common symptom. No serious adverse events due to ARIA-H were reported. However, during open-label extension a lecanemab-treated patient died after receiving thrombolysis for an acute ischemic stroke followed by a symptomatic intracranial hemorrhage[7], and another patient died after having a cerebral hemorrhage while on anticoagulation[8].

cortical superficial siderosis, though enrollment of individuals with 4 or fewer microbleeds was allowed (Table 1).

Paradoxically, even though the anti-beta amyloid monoclonal antibodies are risky to use in CAA, they are also candidate treatments. One can hypothesize that small dosing and slow titration of monoclonal antibodies could allow slow, non-disruptive removal of vascular amyloid, without triggering inflammation and giving time for the vessel wall to repopulate to maintain its integrity, avoiding hemorrhaging. This hypothesis could be tested in clinical trials. However, we reiterate that outside of clinical trials we strongly recommend that, because of the unproven efficacy and the potentially high risk of brain edema and hemorrhaging. anti-beta amyloid monoclonal antibodies should not be used off-label to treat CAA [10].

Although the dawn of disease-modifying therapy for AD should be celebrated, there is a danger of complacency. AD is not solved. Even though the new treatment are highly effective at removing amyloid, functional and cognitive decline is reduced by only 25%−33%, an amount that leads some to question the clinical impact. In our view, a 25% reduction in CDR-SB is clinically meaningful. But our patients want 100% reduction. Refining anti-amyloid treatments may not get us there. What is needed are therapeutic strategies targeting additional pathways, to use in combination with beta-amyloid removal.

We believe that future therapies for AD and other dementias will likely involve personalized, precision combination therapies that include targeting VCID. This should include identifying and treating comorbid cerebral small vessel diseases, and optimizing vascular functions—such as clearance of wastes, neurotropic support, and maintenance of an intact blood-brain barrier—thought to promote brain health and reduce neurodegeneration. Currently, with no FDA or EU approved specific treatments for VCID, we have a long way to go. But with advances in phenotyping and single cell gene expression within the neurovascular unit, and Mendelian randomization approaches that allow stronger causal inferences based on large human genomic datasets, we have better tools to identify novel, potentially modifiable causal pathways. The dawn of effective beta-amyloid therapy should increase, not lessen, the enthusiasm for diagnosing and treating VCID.

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