Conveying risks of harm in Alzheimer's by amyloid lowering

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The recent approval of lecanemab (marketed as Leqembi) by the Food and Drug Administration (FDA) and the expected approval of donanemab later this year for treating patients in the early stages of Alzheimer's disease (AD) dementia present a key challenge for physicians, who must communicate complex results from clinical trials of these drugs to their patients, to help them make decisions on whether treatment benefits outweigh potential risks of harm. Together with the recent announcement of the termination of development and commercialization of aducanumab (marketed as Aduhelm), physicians will be required to not only understand what the published results of trials have established in terms of modest clinical benefits of these drugs, but also consider critical information that remains incompletely disclosed, especially pertaining to the safety of this medication class. Physicians who counsel patients eligible to be treated with these drugs must recognize areas of uncertainty about potential adverse effects due to incomplete reporting of trial results and be able to convey this information to their patients to enable evidence-based decision-making.

The FDA's decision to issue a black box warning for these medications due to amyloid related imaging abnormalities (ARIA) that can cause serious harm due to brain edema (ARIA-E) and micro- or macro-hemorrhages (ARIA-H) in some patients, will be an important consideration when communicating potential risks to eligible patients. The recent announcement that the FDA's anticipated approval of donanemab will be delayed while the agency convenes an advisory committee to further assess safety results underscores the importance of a full understanding of ARIA-related clinical outcomes in patients exposed to this medication class. While such regulatory appraisal and enhanced mechanistic understanding of ARIA through ongoing research is pending, we consider that greater transparency in the reporting of clinical outcomes related to ARIA is important. Deaths related to serious ARIA events have been

reported in patients treated with aducanumab, lecanemab and donanemab [1] [2]. However, peer-reviewed publications reporting results from clinical trials of these drugs have concluded that most cases of ARIA are either asymptomatic or cause only mild symptoms, occur early in the course of treatment, and usually resolve on follow up brain MRI scans [3] [4] [2]. Appropriate use guidelines for lecanemab further underscore this message and recommend that while dosing be suspended in patients who develop symptomatic ARIA, this can be resumed after clinical assessments and monthly MRI scans show resolution of ARIA-E and/or stabilization of ARIA-H after *"a discussion of risks and benefits with the patient and family.* [5]*"*

2.8% of patients in the lecanemab group in the phase-III CLARITY-AD trial showed symptoms due to ARIA (versus 0% in the placebo group) [4]. It is difficult to see how any discussion of risks and benefits in such patients about continued treatment can be meaningfully informed without knowing whether the experience of symptomatic ARIA was associated with accelerated worsening of memory and functional abilities at the end of the trial. It is particularly surprising that none of the published clinical trials of aducanumab, lecanemab and donanemab have yet reported the association between severity of ARIA (both symptomatic and radiological) and clinical outcomes [2-4]. This means that when physicians explain potential risks of amyloid targeting antibodies, they cannot reassure their patients that clinical or radiological resolution of ARIA is a reliable indicator that these will not result in worsening of cognitive or functional abilities with, or without, continued dosing.

Loss of brain volume has been observed with all three monoclonal antibodies targeting brain amyloid accumulation in AD with a recent meta-analysis showing a high correlation between the frequency of ARIA and loss of brain volume [6]. Paradoxically, brain volume loss, including expansion of ventricular spaces in the brain, has been among the most reliable imaging

biomarkers of AD progression [7]. While published results from trials of aducanumab, lecanemab and donanemab have all reported treatment-related loss in brain volume and/or expansion in ventricular volume, they have not addressed whether these changes were related to poorer cognitive and functional outcomes. In the reported results from the phase-III trials of aducanumab, authors noted that expansion of lateral ventricular volume, *"a measure of neurodegeneration"* was observed in all aducanumab treatment groups (low- and high-dose) relative to placebo [3]. A dose-dependent reduction in whole brain volume and increase in ventricular volume throughout the duration of treatment was also reported in the phase-II trial of lecanemab [8] and confirmed in the phase-III CLARITY-AD trial. Similar results have been reported from both phase-II and III trials of donanemab [2,9] . Alternative mechanistic explanations for the observed loss of brain volume induced by amyloid-lowering monoclonal antibodies include a decrease in amyloid plaque volume, cerebral fluid shifts and reduction in periplaque inflammation [10]. Some of these explanations have been advanced to suggest that observed loss of brain volume may represent benign changes similar to pseudoatrophy observed in multiple sclerosis patients treated with disease-modifying drugs. While definitive explanations for these MRI changes may require detailed neuropathological studies, we believe that they should not preclude reporting of associated clinical outcomes at the end of the RCTs.

Finally, while the pivotal phase III trials of these drugs have run for 18 months, this represents a relatively small part of the decade or so that people with mild cognitive impairment (MCI) or mild dementia due to AD will live with their disease. Information about longer-term cognitive and functional outcomes from open-label extension treatment periods and from post-trial surveillance should be made available without undue delay to better inform the risk:benefit discussions that prescribers will have with their patients.

Alongside urging drug-makers to fully report on clinical outcomes related to severity of ARIA and brain atrophy caused by amyloid-targeting monoclonal antibodies and data from treatment and follow-up beyond 18 months, we recommend that practicing physicians clearly outline the areas of uncertainty pertaining to risk of harm from these drugs when they counsel patients considering treatment. We consider that conveying information from incomplete reporting of clinical trials risks endangering patients, undermines faith in physicians and eventually betrays the hope that scientific advances will translate into safe and effective treatments for Alzheimer's disease.

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Competing interests

The authors declare no competing interests.

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