Published Ahead of Print on July 7, 2021 as 10.1212/WNL.0000000000012453

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The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF NEUROLOGY®

Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000012453

Clinical Efficacy, Drug Safety and Surrogate Endpoints: Has Aducanumab Met All of Its Expectations?

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Study Funding:
No targeted funding reported

Disclosure:
L. Hershey is an Associate Editor for *Neurology*. She receives honoraria from MedLink Corp for preparing annual updates. She serves on the Network of Experts Committee for the US Food and Drug Administration.
R. Tarawneh is an Assistant Editor for *Neurology*. She is funded by the National Institute of Aging (R21 AG067755-01A1).

We recently learned that aducanumab has been approved by the US Food and Drug Administration (FDA) for the treatment of Alzheimer disease. As neurologists, we need to carefully review the evidence from the phase 1B and III randomized controlled clinical trials concerning this drug's clinical efficacy and safety in symptomatic persons with mild cognitive impairment or mild dementia who have elevated cerebral levels of amyloid-beta (Aβ). We should also gain an appreciation for how this drug acquired accelerated approval from the FDA based on the surrogate endpoint of Aβ plaque reduction, as measured by PET imaging. We owe this to our patients and to their caregivers.

In this issue of *Neurology*, Salloway and Cummings[1] describe the PRIME trial (phase 1B), where monthly intravenous infusions of high-dose aducanumab showed definite reduction of Aβ on amyloid PET imaging studies. In two identical phase 3 trials, EMERGE and ENGAGE, significant clinical benefit at 78 weeks was only seen in the high-dose group (10mg/kg) of one of these trials (EMERGE). Consistent reduction of Aβ on amyloid PET was observed in both of the phase 3 trials at 78 weeks.

As a counter viewpoint in this issue of *Neurology*, Knopman and Perlmutter[2] argue that the clinical benefit of aducanumab seen in the EMERGE trial was small, amounting to 3 months' worth of delay in clinical decline. They also mention that when results from both phase 3 trials were combined, there were no significant clinical benefits for the high dose. To justify accelerated approval, the FDA relied on a surrogate endpoint, removal of Aβ plaques on amyloid PET. The danger of relying on a surrogate endpoint such as Aβ reduction is that the relationship between Aβ reduction and cognitive improvement is unclear. Several trials with other amyloid reducing drugs have shown no cognitive benefit, and one recent trial actually showed some cognitive worsening [2,3] On the other hand, biomarkers have had an important role in Alzheimer drug development, since compared to cognitive endpoints, they are less likely to be affected by the day-to-day variability produced by mood changes and sleep disturbances.[4]

When it comes to drug safety, Salloway and Cummings[1] mention that the most common adverse effects of aducanumab in EMERGE and ENGAGE were those that have been commonly associated with other amyloid lowering drugs: amyloid related imaging abnormalities with either edema (ARIA-E) or hemorrhage (ARIA-H).[5] In the EMERGE trial, 34% of those in the high dose group experienced ARIA, and in ENGAGE it was 35.5%. Knopman and Perlmutter [2] point out that ARIA adverse events (edema or hemorrhage) were more likely to be seen in those who carried at least one *APOE-e4* allele, a finding that has been observed in previous trials of amyloid lowering drugs.[5] This means that safety monitoring with follow-up MRI scans needs to be

integrated into the routine management of patients who are treated with aducanumab.[2] The most common symptoms of ARIA-E include headache, confusion, dizziness, visual changes, falls, or nausea. One male patient enrolled in ENGAGE was a homozygous *APOE-e4* allele carrier. He developed both ARIA-E and ARIA-H and reportedly experienced clinical symptoms of ARIA-E that lasted about 6 months after the drug was discontinued; nevertheless, signs of ARIA-H persisted.[6]

In summary, before we prescribe aducanumab, we need to explain several things to our patients and their caregivers. First, this drug is intended for those who are in the mild cognitive impairment or mild dementia stage of Alzheimer disease; it was not tested in those with moderate or severe dementia (this is not currently mentioned on the product label).[7] Second, verifying the presence of amyloid pathology in the brain with an amyloid PET scan is recommended, since aducanumab is not intended for treating other types of dementia.[8] Cost and availability of amyloid PET scans could be an issue for patients with limited resources and those who live in rural areas. Amyloid PET scans typically cost between $5000-7000 per study and are not reimbursed by third party payors.[8] Third, *APOE-e4* screening, baseline MRI and follow-up MRI are all important for predicting the risk of ARIA adverse events (increased risk of ARIA with *APOE-e4/e4* was not mentioned on the product label).[7] Fourth, the price of aducanumab is considerable (wholesale acquisition costs are currently $4312 per monthly infusion for a 74kg patient at the 10mg/kg dose).[7] Fifth, no stopping rules are currently provided in the drug label, but the AAN recommended that an "outcomes-based payment arrangement" should be worked out in the future with third party payors.[8] Finally, the patient and their caregivers need to understand that the clinical benefits of aducanumab are small and that more data will be needed in the future to determine whether these benefits are clinically or functionally meaningful to patients (a new clinical trial has been recommended by the FDA to Biogen to resolve these questions).[7] We look forward to seeing these new data.

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