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NEWS

Aducanumab: Appropriate use recommendations

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1 | SUMMARY LEAD

Aducanumab recently received accelerated approval by the FDA. An Expert Panel was comprised to provide recommendations on appropriate use of aducanumab in real world practices. Patient selection, aducanumab administration and monitoring, management of ARIA, and best practices in patient care in the context of aducanumab therapy are described. The paper was published in the *Journal of Prevention of Alzheimer's Disease*.[1]

2 | RESEARCH NEWS

The approval of aducanumab (Aduhelm) by the US Food and Drug Administration (FDA) provides a new therapeutic option for patients with Alzheimer's disease (AD). Aducanumab is an amyloid-targeting monoclonal antibody. Approval was "accelerated" based on reduction of amyloid plaques observed in patients treated with aducanumab. Plaque reduction was deemed reasonably likely to predict clinical benefit. Continued approval may be contingent on verification of clinical benefit in confirmatory trials. The pivotal trials leading to the approval of aducanumab included participants with mild cognitive impairment (MCI) due to AD or mild AD dementia comprising an "early AD" population. The population comprises stages 3 and 4 of the FDA staging system.[2] In all participants, the presence of brain amyloid was confirmed by amyloid positron emission tomography (PET). The updated Prescribing Information describes the indication for aducanumab as for the treatment of Alzheimer's disease and instructs that treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease.[3] The Prescribing Information[3] does not mandate amyloid biomarkers to confirm the diagnosis and the presence of the amyloid target for use of aducanumab. Discussion among experts in drug development, clinicians who care for patients with AD, experts in magnetic resonance imaging (MRI), and leaders involved in aducanumab clinical trials led to formation of an Expert Panel working group to develop recommendations for Appropriate Use of aducanumab (Cummings, Aisen, Atri, Apostolova, Salloway, and Weiner.)[1] The goals of the Expert Panel were to provide broader guidance with more detailed information than presented in the Prescribing Information[3] for practicing clinicians on: how to choose patients for treatment using criteria that are aligned with the characteristics of the participants in the clinical trials; what to discuss with patient-care partner dyads in order to facilitate patient-centered informed decisions regarding aducanumab; how to provide aducanumab safely, especially regarding monitoring, detection and management of amyloid related imaging abnormalities (ARIA); and how to define best practices for integrating aducanumab into AD care.

The Expert Panel recommended the following features for patients appropriate for treatment with aducanumab:

- Clinical diagnosis of MCI due to AD or mild stage AD dementia after a comprehensive evaluation
- Cognitive assessments that include validated instruments and with performance scores of 21 or higher on the Mini Mental State

Examination (MMSE) or an equivalent validated test. The range of MMSE scores of trial participants was 24-30; test-retest reliability of the MMSE is 3 points suggesting that a score of 24 is indistinguishable from a score of 21. The Montreal Cognitive Assessment (MoCA) is an alternative for the MMSE; the appropriate population would include patients with MoCA scores of 17 and above. Formal neuropsychological testing can provide information to support the cognitive assessment.

- Amyloid positive by PET or an AD signature pattern on cerebrospinal fluid (CSF) testing
- Stable medical and cardiovascular/cardiopulmonary conditions; no organ failure; and no active cancer (low grade basal and squamous cell carcinomas excepted)
- Psychiatrically stable
- Not on anticoagulants and no coagulopathy present
- Can be on cholinesterase inhibitors and memantine
- Testing for apolipoprotein genotype is optional and dependent on discussion with the patient and care partner. Patients should be informed of the increased risk of development of ARIA associated with being an apolipoprotein E $\in$ 4 gene carrier when treated with aducanumab.
- Neurological examination consistent with AD, without evidence of any other neurological disorder
- Baseline MRI with no evidence of acute or subacute hemorrhage, macrohemorrhage, greater than 4 microhemorrhages, cortical infarction (>1.5 cm), 1 lacunar infarction (≥1.5 cm), >1 area of siderosis, or diffuse white matter disease.
- Patient and care partner recognize the nature and requirements of therapy (eg, monthly infusions) and the expected outcome of therapy (slowing of decline without cognitive or functional improvement)

The Expert Panel described the requirements of aducanumab administration including monthly infusions beginning with a dose of 1 mg/kg for the first and second infusions; advancing to 3 mg/kg for infusions three and four; increasing to 6 mg/kg for the 5th and 6th infusions; and reaching the intended dose of 10 mg/kg on the seventh infusion. The target dose level of 10 mg/kg is continued for the foreseeable future.

The Expert Panel recommended structured monitoring for amyloid-related imaging abnormalities of the effusion (ARIA-E) or hemorrhagic (ARIA-H) type. MRIs should be obtained at least 1 year prior to the initiation of treatment or at baseline if there are any suggestions of a focal brain event since the last MRI; and again prior to the fifth, seventh, and 12th infusions. Given the prevalence of ARIA-E with the 10 mg/kg dose in the phase 3 studies, especially among APOE-4 carriers, clinicians may consider an additional MRI before the 10th dose, after three doses of 10 mg/kg have been administered, to maximize detection of ARIA. In addition to these scheduled MRIs, patients should have an MRI whenever their evaluation has elements suggestive of ARIA; these include headache, vomiting and/or nausea, confusion, dizziness, visual disturbance, gait difficulties, loss of coordination, tremor, transient ischemic attack, new onset seizures, or significant and unexpected acute cognitive decline. MRI studies for ARIA should include FLAIR, T2* GRE and quick DWI.

If ARIA (ARIA-E or ARIA-H) is symptomatic, treatment should be suspended, and a comprehensive clinical assessment performed. MRI should then be repeated monthly; if symptoms resolve and the ARIA-E resolves or the ARIA-H stabilizes, treatment can be resumed. Patients who have severe symptoms (eg, seizure, stroke-like syndromes) should permanently discontinue aducanumab treatment.

If ARIA (ARIA-E or ARIA-H) is asymptomatic, the MRI is reviewed to determine if the ARIA is mild, moderate, or severe (applying definitions in the Prescribing Instructions and the Appropriate Use recommendations). Severe and moderate ARIA are managed using the same strategies described for symptomatic ARIA; treatment is paused and is re-initiated only if ARIA-E resolves or ARIA-H stabilizes. Dosing can be continued in mild ARIA that is asymptomatic but should be monitored with monthly MRIs.

Non-ARIA side effects must be monitored; those observed in trials included headache, falls, and diarrhea.

Efficacy in the clinical trials was monitored with a battery of global, cognitive, functional, and behavioral instruments. Use of these instruments may be unsuitable for the workflow of many clinical practices. Effectiveness monitoring tools recommended by the Expert Panel included the MMSE, MoCA, or an equivalent valid and reliable cognitive test; AD8 for global assessment; Functional Activities Questionnaire (FAQ) for functional assessment; and the Neuropsychiatric Inventory Questionnaire (NPI-Q) for behavioral evaluation. In practices with access to neuropsychologists, more extensive evaluations may be pursued.

Best practice for providing aducanumab therapy is to adopt a patient-centered focus. Patients and care partners require information and counseling regarding the disease state, clinical uncertainties, multidimensional care strategies, and the potential benefit and harm of aducanumab. This includes an open, honest, and comprehensive discussion regarding the possible effects of aducanumab on removal of amyloid plaques; uncertainties regarding expectations for mitigation of clinical decline; potential side effects including likelihood and nature of ARIA and of serious ARIA-related symptoms in those treated with 10 mg/kg; and the need for long-term treatment monitoring and adherence. Referral to the Alzheimer's Association (www.alz.org) and other trusted sources can assist the clinician in providing reliable information.

Decision support frameworks for responding to the challenges raised by aducanumab are described. These include how best to inform patients when therapy should be stopped (because of ARIA, lack of adherence, progression to moderate-severe AD dementia, etc). Strategies are needed for informing patients with preclinical AD who are known to have positive amyloid studies that the Expert Panel recommends not treating with aducanumab until more data are available. Similarly, there is no information on the use of aducanumab in patients with moderate to severe AD (FDA stages 5 and 6), and the Expert Panel recommends against initiating aducanumab treatment in patients in these more advanced stages of AD. The

Expert Panel recommends against treating amyloid positive patients with Down syndrome, dementia with Lewy bodies, or cerebral amyloid angiopathy with aducanumab. The Expert Panel recommends caution in treating patients with autosomal dominant AD and those with atypical AD syndromes until more data are available; the lack of information in these settings should be disclosed to potential treatment candidates. We are the beginning of the aducanumab era, and more data will inform the range of appropriate use of this agent.

Persons from underrepresented communities require access to aducanumab to ensure equity of treatment availability. Effort must be expended to engage diverse populations in discussions of cognitive impairment, AD, and the availability of appropriate diagnosis, treatment, and care.[4]

Aducanumab is an unprecedented therapy; it is the first drug approved for treatment of AD based on demonstration of plaque lowering and the first addressing the underlying pathophysiology of AD. Clinicians, patients, care partners, and stakeholders of the healthcare system must adjust to the new therapeutic circumstances. The goal of the Expert Panel was to provide early guidance on the appropriate use of aducanumab in this redefined treatment environment.

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CONFLICT OF INTEREST

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REFERENCES

1. Cummings J, Aisen P, Apostolova LG, et al. Aducanumab: appropriate use recommendations. *J Prev Alzheimers Dis*. 2021. In Press.
2. Food and Drug Administration. Early Alzheimer's Disease: Developing Drugs for Treatment Guidance for Industry. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). February 2018.
3. U.S. Food & Drug Administration Drugs@FDA: FDA-Approved Drugs. Aducanumab. 2021. Reference ID 4822820 https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=761178
4. Babulal GM, Quiroz YT, Albensi BC, et al. Perspectives on ethnic and racial disparities in Alzheimer's disease and related dementias: update and areas of immediate need. *Alzheimers Dement*. 2019;15:292-312.