The Geriatrician, the Primary Care Physician, Aducanumab and the FDA Decision: From Frustration to New Hope

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Alzheimer is a severe disease and new therapies are really needed. After the development of symptomatic drugs 30 years ago, our objective is to develop disease modifying treatment using anti-amyloid therapies over an 18-month period. First we targeted mild to moderate AD, probably at a too severe stage. Later we targeted mild dementia and when biomarkers became available, we realized that almost 30% of our patients had no amyloid deposit and probably did not have Alzheimer's disease (1, 2). Then, we started to target early and mild AD defined with amyloid deposit using CSF and PET biomarkers, but our drug dosage was probably not high enough (3, 4). And finally with the Aducanumab studies we observed some effects with high doses (5, 6). On June 7, 2021 for the first time, the FDA approved a disease modifying drug, Aducanumab. After decades of research, it is good news for patients, and those dedicated to the field, but it is also a challenging time with some frustrations and some hope. In the present JNHA editorial we will review the FDA statement and the consequences for geriatricians and primary care physicians, from frustration to new hope.

FDA statement on Aducanumab

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf:

For the FDA "ADUHELM is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with ADUHELM. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s). The recommended maintenance dosage by the FDA is 10 mg/kg administered as an intravenous infusion over approximately one hour every four weeks (1). FDA recommend to obtain a recent (within one year) brain MRI prior to initiating treatment as well as prior to the 7th and 12th infusions. If ARIA-H is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates stabilization (1). The safety of ADUHELM has been evaluated in 3,078 patients who received at least one dose of ADUHELM. The efficacy of ADUHELM was evaluated in two double-blind, randomized, placebo-controlled, parallel group studies (Study 1, NCT 02484547

and Study 2, NCT 02477800) in patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology and mild cognitive impairment or mild dementia stage of disease). The mean age at study entry was 70 years (range from 50 to 85). ADUHELM reduced amyloid beta plaque in a dose- and time-dependent manner in Study 1, Study 2, and Study 3, compared with placebo. The magnitude of reduction was time- and dose-dependent. ADUHELM reduced markers of tau pathophysiology (CSF p-Tau and Tau PET) and neurodegeneration (CSF t-Tau) in Study 1 and Study 2. In Study 1, 1638 patients were randomized 1:1:1 to receive ADUHELM low dose, ADUHELM high dose, or placebo. The primary efficacy endpoint was the change from baseline on the CDR-Sum of Boxes (CDR-SB) at Week 78. In Study 1, treatment with ADUHELM high dose demonstrated reduced clinical decline, as evidenced by a statistically significant treatment effect on change from baseline in CDR-SB compared to placebo (-0.39 [-22%], $p = 0.0120$). The estimate of the treatment effect favored ADUHELM across all prespecified subgroups of interest. Secondary efficacy endpoints included the change from baseline in MMSE score at Week 78, the change from baseline in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) (ADAS-Cog 13) at Week 78, and the change from baseline in the Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (Mild Cognitive Impairment version) (ADCS-ADL-MCI) score at Week 78. In Study 1, statistically significant differences from placebo were observed in the ADUHELM high dose group on all secondary efficacy endpoints evaluated. The estimate of the treatment effect favored ADUHELM across most prespecified subgroups of interest for the secondary efficacy endpoints. The Neuropsychiatric Inventory-10 item (NPI-10) was the only tertiary endpoint that assessed efficacy. In Study 2, 1647 patients were randomized 1:1:1 to receive ADUHELM low dose, ADUHELM high dose, or placebo. No statistically significant differences were observed between the ADUHELM-treated and placebo-treated patients on the primary efficacy endpoint, the change from baseline in CDR-SB score at 78 weeks. In Study 3, 197 patients were randomized to receive a fixed dose of ADUHELM 1 mg/kg ($n=31$), 3 mg/kg ($n=32$), 6 mg/kg ($n=30$), 10 mg/kg ($n=32$), titration of ADUHELM to 10 mg/kg over 44 weeks ($n=23$), or placebo ($n=48$) for 12 months. Clinical assessments in Study 3 were exploratory. Results for clinical assessments were directionally aligned with the findings from Study 1, with less change from baseline in CDR-

SB and MMSE scores at 1 year in the ADUHELM 10 mg/kg fixed-dose group than in patients on placebo (CDR-SB: -1.26, 95% CI [-2.356, -0.163]; MMSE: 1.9, 95% CI [0.06, 3.75]). FDA recommend to inform patients that ADUHELM may cause Amyloid Related Imaging Abnormalities or “ARIA”.

What Aducanumab and the FDA decision can bring to geriatric and primary care physicians ?

Frustration

The effect of Aducanumab on Alzheimer has been recognized by the FDA and appears to be real and related to high doses. It needs close MRI follow-up and clinical confirmation on the long-term effect (6). The patient mean age in the clinical trials was 70 years, with probably few over 80yrs, frail or with comorbidities (6). A new long-term (9 years) study is required by the FDA to clarify the clinical long-term effects of the drug. Frailty status was not measured in the Aducanumab trial, like in most ongoing Alzheimer trials with similar ongoing drugs. Safety will likely be more problematic in the frail older adults. It will be difficult to prescribe such a drug for the typical frail old adult patients with comorbidities usually seen in geriatric clinic. Limited access to MRI and infusion facilities will also become a problem. Moreover, many geriatric patients have mixed dementia including vascular lesions, and an advanced stage of the disease with severe dementia. For this reason, most of the geriatric, primary care physicians, patients and caregivers will no doubt be frustrated and the drug will be limited to a small proportion of patients in a few centers. However, it is not due to the FDA or the drug, but it is the fact that, until now very little has been done to promote healthy aging, and most geriatricians see patients with severe dementia and comorbidities. It is time to change this, as we did when we highlighted few years ago the importance of moving geriatric medicine to emphasize frailty and pre-frailty (7, 8).

New Hope

For the W.H.O organization, healthy aging is not a life without diseases, we can have diseases at any age; but healthy aging is when we are able to maintain our functions to be able to do what we value (9). Its Integrated Care for Older People (ICOPE) program recommends to screen for intrinsic capacities decline in older adults including cognition. The global aim is to prevent frailty for the robust and to prevent dependency for the frail (10). ICOPE Monitor (11-13) gives us the opportunity to monitor intrinsic capacities remotely and to intervene earlier. Alzheimer blood biomarkers (eg. P-tau 217) are currently almost validated (14-16) and will soon come to our practice. Combining digital medicine (eg. ICOPE Monitor) and blood biomarkers must allow us to diagnoses early AD in primary care and give access to new therapies for these subjects. Aducanumab is the first, but several other drugs are in development (17, 18) and will likely become available shortly as well as other drugs with different targets. We must

use the FDA decision as a challenge to be prepared and to move our practice to prevention and early diagnosis (19) for our old patients. Alzheimer's is responsible for a large part of the dependency with advancing age, we must find the way to be part of the game, not too late, not too soon, but at the right time, and be ready for the next drug generations.

Conflict of interest: Dr. Vellas reports grants from Lilly, Merck, Roche, Lundbeck, Biogen, grants from Alzheimer's Association, European Commission, personal fees from Lilly, Merck, Roche, Biogen, outside the submitted work.

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How to cite this article: B. Vellas. The Geriatrician, the Primary Care Physician, Aducanumab and the FDA Decision: From Frustration to New Hope. *J Nutr Health Aging*. 2021;25(7):821-823; <http://dx.doi.org/10.1007/s12603-021-1657-8>