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Editorial

The 'Aducanumab Story': Will the Last Chapter Spell the End of the 'Amyloid Hypothesis' or Mark a New Beginning?

[Deng Xiaoping said, "It doesn't matter if a cat is black or white, so long as it catches mice". In the same vein, the blemishes in the pivotal studies of Aducanumab do not matter, so long as it fixes cognitive impairments]

Z.S. Khachaturian

Corresponding Author: Zaven S. Khachaturian, PhD., Campaign to Prevent Alzheimer's Disease [PAD2020] Potomac, MD 20854, M: 301-602-4504, E: zaven@pad2020.orgt

The paper entitled "Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease" by Budd Haeberlein, S., Aisen, P., Barkhof, F. et al in the current issue of J Prev Alzheimers Dis [https://doi.org/10.14283/jpad.2022.30] presents the much-anticipated results of two pivotal trials to demonstrate the safety and efficacy aducanumab as a therapy for early-stage Alzheimer's disease [AD]. This phase 3 study shows a reduction of molecular imaging and biofluid markers of AD is associated with a slowing of cognitive decline.

These results received an accelerated approval by FDA in June 2021 based on the drug's effect on a surrogate endpoint that is '…reasonably likely to predict a clinical benefit to patients …' (1). This 'conditional' regulatory ruling requires further confirmatory [phase-4] trials to verify that drug effect on the surrogate endpoints actually predicts a clinically meaningful benefit. The subsequent decisions by EMA [in the EU] and the CMS [in the US] have not been favorable for the routine clinical use of this drug for treatment of dementia-AD.

These landmark regulatory determinations by FDA, EMA and CMS have created controversy with passionate debates regarding: the methodological flaws of the two pivotal trials, questionable scientific rational, weak association between surrogate marker and cognitive function, financial implication of high cost of treatment and the uncertainty of the ultimate clinical utility; pending validation of a clinically meaningful benefit for the patient (2).

Regardless of the various stances in ongoing debate over the regulatory ruling and the clinical merits of aducanumab, it is important to publish the results of the first phase-3 trial to show a putative association between a surrogate marker and a behavioral/clinical feature of dementia-AD. This study, and the ensuing 'conditional' regulatory decision, is a significant 'teaching' milestone in the 40-year struggle to develop effective disease-modifying interventions of dementia-AD.

Heated debates over controversial issues in science is not a new phenomenon or necessarily detrimental to progress. For example, nearly thirty years ago the study and the regulatory ruling regarding Tacrine, the first drug approved for AD, was also controversial. [DOI: 10.1177/106002809402800612]. The study was plagued with methodological problems; adverse events [re: liver toxicity] halted the trial before completion and as in the present situation FDA was concerned with the adequacy/validity/relevance of the outcome measures. Eventually by 2013 Tacrine [Cognex] was withdrawn from the market due to its limited clinically meaningful benefit and concerns over its link to liver toxicity. But, Tacrine was an important 'teaching event' in the history of therapy development for AD.

In retrospect one of the important aspects of the Tacrine experiences was the fact that FDA set the regulatory hurdle-requirement for approval at 'just right' level, which might be the case in the debate over the pros and cons of the conditional approval the aducanumab. Thirty years ago, if the FDA's 'regulatory-bar' for Tacrine was set too low, it would have encouraged the development of a plethora of junk treatments with questionable efficacy. On the other hand, a higher 'regulatory-bar' would have stifled further R&D on alternative putative interventions based on the cholinergic hypothesis. Now, both the FDA-CMS regulatory decisions regarding aducanumab might be the 'just right' level of regulatory hurdle-requirement for a complete approval. In the final chapter of 'story' it turned out that Tacrine was not an ideal drug, but its legacy paved the way to further research on improved drugs.

So, the good news about aducanumab is that [even if in the long run it fails the promise of becoming treatment of choice], the FDA's conditional approval has already created an encouraging environment for further investments in R&D of drugs in this class. But, the bad news is the challenge facing aducanumab in addressing the need for strong compelling evidence [e.g., a big drug effect (3)] to validate the regulatory premise for the conditional approval; namely the assumption that

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'…a change in surrogate endpoint due to a drug effect may be considered "reasonably likely to predict" an actual clinical benefit…'. Thus far the available evidence to support this assertion, which is a key rationale for accelerated approval, has been questionable. The result of two pivotal studies reported by Haeberlein on the efficacy of aducanumab show a very 'weak signal' for the association between '…reduction of molecular imaging and biofluid markers of AD ' and ' a slowing of cognitive decline…'. The fly in the ointment for aducanumab and other drugs in the same class is the delivery of convincing evidence for the promissory note that changes in surrogate marker do in fact predict decrements in one or more clinically meaningful outcome [e.g., cognitive impairment].

Now, the question is how to weigh FDA-CMS decisions as teaching lessons about potential pitfalls in developing therapy.

In the ongoing debate about the methodological flaws of the two pivotal trials' study design, the questions about the extent of aducanumab's effectiveness in reducing amyloid fibril burden as a surrogate index of the disease is not the crucial issues but rather it is the uncertainty of whether or how this drug will meet the patients' needs for effective treatments of a memory disorder. The vital unknown is whether aducanumab [and/or other agents of that class] will delay, slow-down or stop the progressive deterioration of one or more clinical/behavioral feature of dementia [e.g., cognitive decline].

The essential take-home message from FDA-CMS decisions is the importance of interventions that impact on daily functions or life experiences, independent functioning ADLs, lifestyle or quality of life issues], rather than merely the removal of brain lesions that may not correlate well (if at all), with the defining behavioral/clinical features of the actual experience dementia-Alzheimer syndrome.

The regulatory decision about aducanumab, a conditional approval, was based on supposition that a surrogate endpoint may be used as an index for potential prediction of a clinical benefit. In the controversy surrounding this ruling it is important to remember the fact that a surrogate marker is not itself a measure of clinical benefit. Therefore, the important need for a phase-4 confirmatory trials to confirm the assertion that aducanumab's effect on the surrogate endpoint actually predicts accurately/reliably a clinically meaningful benefit to the patient. If such a confirmatory trial fails to verify sufficient clinical benefit, the FDA may withdraw the market approval or require changing the label for indication.

What if the prospective phase 4 confirmatory trial fails to demonstrate efficacy of aducanumab to yield a clinically meaningful outcome or proves to be of limited benefit to a small subset of larger universe of people with dementia? What are some alternative strategies for clinically meaningful interventions that should receive greater attention and emphasis?

On the other hand, if the strategy of using the drug's effect on surrogate marker as an index for efficacy proves to be effective in predicting a clinically meaningful outcome, there will be the need to explain the precise mechanism of action of this intervention; i.e., the molecular signaling pathways for maintaining or restoring neuronal functioning that underlie the behavior-cognitive impairment. Better understanding of aducanumab's mechanism of action on neuronal function [e.g., maintaining synaptic vitality] will provide the critical knowledge for improvements or developing alternative interventions to modulate the signaling pathways that mediate the behavior.

The selection of the 'right target' and the 'correct agent' for interventions that result in clinically meaningful outcome remains to be the vital challenge for dementia research (3, 4). For example, the problem with the strategy of focusing on hallmark lesions of the disease as the primary target along with the uses the class of 'agents' like aducanumab is the inconsistent relationship between biological phenotypes of the disease pathogenesis and clinical/behavioral features. Another difficulty for this approach to treatment is due to the fact that these lesions can also be advances in cognitively intact individuals. The connection between the 'disease' and amyloidosis, tauopathy, and other markers of pathology have been known for some time, along with several theories about the toxicity of these lesions. However, the precise molecular mechanisms of action or exactly how these misfolded proteins effect neuronal function remain unknown. Thus, one of the drawbacks of putative treatments based on toxicity of misfolded protein is that these therapeutic strategies do not offer a clear account of the full cascade of biological signals [i.e., specific signaling pathways] that are necessary, and sufficient to mediate a 'drug effect' that affects behavioral and ameliorates clinical features-symptom of dementia. Thus, the precise cascades of multiple potentially interwoven signaling pathways, triggered by various biological signals [including but not limited to mis- folded protein components of hallmark lesions] leading to synaptic dysfunction and eventually massive loss of synapses, remain poorly understood. Key postulated mechanisms have yet to be verified, or even identified.

Among core neuropathological features of dementia-Alzheimer syndrome that has not been adequately exploited as a primary therapeutic target is the progressive-massive loss synapse loss and pruning of dendritic arbor/microglial synaptophagy. The irony is that loss of synaptic connectivity is invoked in one way or another by virtually all major ideas on the origin of the disease. This aspect of the neuropathology, which is the most proximal neurobiological event that underlies the clinical features of the disease, provide the best parsimonious account for the link between brain biology and behavior. Moreover, synaptic dysfunction is the common thread for the integration of various ideas about the underlying neurobiology

of various neurodegenerative disorders. Therefore, path to explain the mechanistic relationship between cognitive impairment in dementia and the neurobiology underlying such clinical features must come through explanation of how particular neural networks-systems fail.

In conclusion, the fact remains that business as usual, prevailing ideas about pathogenesis and current paradigms for therapy development have not been very productive after 40-years of massive investments in research. The important lesson from FDA-CMS decisions is the need to adopt new-different ideas, assumptions and directions for therapy development (4, 5). As the search for alternative therapeutic targets-paradigms proceeds, it is important to be mindful about the fact that in the long history of the planet the primary complaint of all patients with dementia is not '…too much amyloid or tau in the brain…' but rather it is the ailments of cognitive impairment, depression, sleep disturbance, agitation, confusion etc., that require effective and lasting fixes; thus these are the essential targets for therapy development.

Conflict of interest: ZS Khachaturian is: Editor-in-Chief, Alzheimer's & Dementia: The Journal of the Alzheimer's Association; Senior Science Advisor: Alzheimer's Association; President of Prevent Alzheimer's Disease 2020 [PAD2020.org]; Member of board: Care Weekly / Khachaturian & Associates Inc.; Received reimbursement – for travel to meeting: Alzheimer's Association and Acadia Pharmaceuticals /for participation on an Ethics Advisory meeting: Biogen.

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