Meeting Report:
Making the Case for Accelerated Withdrawal of Aducanumab

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Abstract

The controversial approval in June 2021 by the Food and Drug Administration (FDA) of aducanumab (marketed as Aduhelm), Biogen's monoclonal antibody for patients with Alzheimer's disease, raises significant concerns for the dementia field and drug approval process, considering its lack of adequate evidence for clinical efficacy, safety issues, and cost. On 15 December 2021, an international group of clinicians, basic science experts, psychological and social science researchers, lay people with lived experience of dementia, and advocates for public health met to discuss making a recommendation for whether aducanumab's approval should be withdrawn. Attendees considered arguments both in favor of and in opposition to withdrawal and voted unanimously to recommend that the FDA withdraw its approval for

aducanumab and to support the Right Care Alliance's filing of a formal Citizen Petition to this effect.

Introduction

Background

Aducanumab (marketed as Aduhelm in the US), is a human immunoglobulin gamma 1 (IgG1) monoclonal antibody developed by Neuroimmune (Switzerland) in partnership with Biogen that has high affinity for a conformational epitope on aggregated forms of Aβ. Phase Ib trials published in 2016 demonstrated the capacity of aducanumab to reduce amyloid plaque in the human brain. Two phase III trials—ENGAGE and EMERGE—enrolled participants with early Alzheimer's disease (AD), but both were discontinued in March 2019 after a futility analysis. In late 2019, Biogen presented post hoc analyses, based on approximately 55% of patients in both trials having completed their treatment, and subsequently filed a Biologic Application License with the Food and Drug Administration (FDA) who recommended consideration for marketing approval.

In November 2020, the FDA Peripheral and Central Nervous System Drugs Advisory Committee (including two of the authors of this Report, ASK and GCA) voted nearly unanimously not to recommend the approval of aducanumab for the treatment of early AD (10 opposed, 0 in favor, 1 undecided). In June 2021, contrary to the recommendation of their own advisory committee and the FDA Office of Biostatistics, the FDA granted aducanumab Accelerated Approval for marketing. This decision was based on a surrogate marker, i.e., the lowering of amyloid plaque burden on PET scan being "reasonably likely" to predict clinical benefit.

Rationale for the meeting

In the wake of FDA's decision and ongoing concerns about efficacy, safety, and cost of the biologic, a group of international researchers, clinicians, and policy experts met on 15 December 2021 to discuss making a case for accelerated withdrawal of aducanumab. The plan was to consider arguments available in the literature, media, and from other experts both for and against such a proposal

Meeting summary

Arguments for requesting accelerated withdrawal

1. Lack of evidence for efficacy

Participants considered that the most persuasive argument for withdrawal was lack of evidence for clinical benefit associated with aducanumab therapy.

2. Concerns about safety

Given the lack of clear efficacy from the ENGAGE and EMERGE trials, the serious side effects linked with the treatment assumed greater importance. Frequent side effects included blurred vision or other changes in vision, confusion, dizziness, falls, hallucinations, and headache. Participants noted serious adverse effects, including *A*myloid-*R*elated *I*maging *A*bnormalities (ARIA), i.e., brain edema, micro-hemorrhages, and superficial siderosis. Reportable Serious Adverse Events have included at least one death potentially linked to aducanumab, but this event and other associated deaths were still under investigation at the time this meeting report was drafted.

3. Concerns about the FDA's Accelerated Approval process

Participants considered the FDA's use of plaque reduction on amyloid PET scans as a surrogate clinical endpoint for treatment benefit to be unsupported by scientific evidence. A consistent relationship between amyloid plaque reduction via PET scan and a meaningful clinical benefit has not been established

4. Other concerns about the process at the FDA

The group discussed more general concerns about the process leading to the consideration of aducanumab, specifically the closeness of relationships between the regulators and the company, and the influence of the Alzheimer's Association. They noted that at the time of the meeting, the Inspector General and two congressional committees were investigating some of these matters. The group expressed concern that these potential improprieties unduly influenced the approval decision. The group also raised more general concerns that the Accelerated Approval process itself had been misapplied in this and other cases and served the interests of industry more than patients. Since the meeting, the Securities and Exchange Commission, Department of Health and Human Services, and the Federal Trade Commission have announced investigations into this and potentially other uses of Accelerated Approval process at the FDA.

5. Cost and opportunity costs

The initial announced price of the drug at about $56,000 fro an individual of average weight (subsequently reduced to $28,200 per year) was considered by the group to be excessive and well beyond all prior estimates. Participants recognized that the FDA cannot consider potential cost as a part of its approval process. However, the group also recognized that letting the FDA decision stand would diminish attention, and potentially funding, for other pharmacologic, as well as psychosocial and public health interventions

that would likely provide greater benefit to patients living with dementia and society at large.

6. Risk of overmedicalization

Participants expressed concern over the reliance on biomarkers to establish disease as a condition defined primarily by its biology rather than its clinical features. The potential for overdiagnosis and overtreatment of Mild Cognitive Impairment and AD was noted.

7. Loss of credibility for the FDA

There was fairly consistent agreement from domestic and international participants that the approval of aducanumab represented an example of poor regulatory judgment that has weakened the national and international credibility of the FDA. Of note the European Medicines Agency (EMA) refused marketing authorization for aducanumab on the 16th December 2021.

8. Implications for future drug development in AD

Participants believed the Accelerated Approval decision could also have major negative ramifications for future drug development. Although participants were unsure of whether lowering the bar for approval would affect the development of new drugs and biologics for dementia, there was strong concern that the arguments claiming this approval would foster innovation were not convincing.

Arguments against requesting withdrawal of the FDA Accelerated Approval

In advance of the meeting, some participants sought reasons against advocating for withdrawal from other experts, media, and the literature. Some argued that we should wait for the appointment a new FDA Commissioner (Janet Woodcock was interim at the time of the meeting) to have more impact. Others suggested that post-approval processes like assessment by payors, decisions of health care systems, skepticism from potential prescribers, emergent safety issues, patient and family reluctance, and competition from other drugs would likely limit the use of the drug. Participants in the meeting did not find any argument persuasive enough to change the group’s position to call for withdrawal.

Participant recommendations, meeting outcome

Attendees voted unanimously to: (1) issue a formal statement calling on the FDA to withdraw approval of aducanumab and (2) support the filing of a Citizen Petition to the FDA by the Right Care Alliance calling for withdrawal.

That statement as posted online is presented below.

Expert statement

We call on the FDA to withdraw its marketing approval for aducanumab for the treatment of Alzheimer's disease. An accelerated withdrawal would mitigate some of the harm of its unwarranted Accelerated Approval for these reasons:

1. Aducanumab failed to demonstrate clinical benefit for patients and did not meet the FDA's 2019 guidance criteria for a regular approval of substantial effectiveness. In two terminated trials, one showed no effect, while the other showed an effect that was not clinically meaningful.
2. Aducanumab also did not meet the FDA's own criteria for accelerated approval based on surrogate markers because amyloid plaque does not correlate with clinical ratings, severity of disease or progression. The FDA's claim that a reduction in amyloid plaque is "reasonably likely to predict" such a benefit is without foundation.
3. Given the lack of evidence for clinical benefit, the risks of aducanumab are unacceptable. This drug causes high rates of potentially dangerous side effects (disorientation, falling, brain swelling and bleeding) and a risk of death that is yet to be defined.

We are deeply concerned about broader issues raised by the approval of this drug. The FDA's acceptance of amyloid plaque PET scans instead of actual patient improvement for approving drugs for Alzheimer's disease is not scientifically well-founded. In the absence of evidence of meaningful clinical benefit, the continued availability of aducanumab may to lead to widespread overtreatment that will not improve the quality of life of patients, will expose them to unnecessary harms, and will consume extensive resources better spent on supportive services and public health measures to help people with this potentially devastating disease.

The FDA's decision to approve aducanumab is indefensible in both scientific and clinical terms. This drug should be withdrawn from the market immediately.

Conclusion

There are strong arguments in favor of the FDA quickly withdrawing aducanumab from the market. Events after the December 15th meeting, including the Centers for Medicare & Medicaid Services (CMS) restrictive coverage decision (which limited payment to participants in qualifying clinical trials), further regulatory and congressional investigations, and the preponderance of subsequent expert and public commentaries have reinforced the stated position of this group.

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Position paper can be found at (accessed 2-26-22)

https://rightcarealliance.org/call-for-the-accelerated-withdrawal-of-aducanumab-aduhelm/