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Opinion

Aducanumab for Alzheimer's disease: A regulatory perspective

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ABSTRACT

On June 7th 2021, the Food and Drug Administration (FDA) granted approval for Aduhelm (aducanumab) for the treatment of Alzheimer's disease under its accelerated approval program. Aducanumab is the first putative disease-modifying therapy (DMT) approved for the treatment of AD with a great potential for clinical benefit over current symptomatic therapies. The scientific community has been largely confounded by this historical decision since this has been based on the reduction of a surrogate marker (amyloid beta) and not on data showing clinical efficacy. Here we provide a regulatory perspective on the topic and discuss potential similarities and differences between the FDA's and EMA's evaluative processes.

1. Introduction

The Food and Drug Administration (FDA) has recently granted accelerated approval for Aduhelm (aducanumab) (https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug), the first putative disease-modifying therapy (DMT) approved for the treatment of Alzheimer's disease (AD). Aducanumab is a human monoclonal antibody able to reduce, in a dose- and time-dependent manner, brain amyloid β (Aβ) plaques as measured by PET imaging studies. The targeting of Aβ by aducanumab provides support to the classic amyloid cascade hypothesis [6], which has never been universally accepted. Indeed, despite biomarker data indicate target engagement, clinical data show that the drug failed to protect patients from cognitive and functional decline. This is why the Alzheimer's scientific community has been somehow confounded by this approval decision (https://www.nature.com/articles/d41586-021-01546-2), especially in the current frame of precision medicine in AD. Indeed, this paradigm provides a conceptual basis to overcome the limitations of traditional "one-size-fits-all" magic bullet in these highly heterogeneous target populations [5]. Therefore, in line with this approach, future trials should consider patient stratification according to demographic, clinical, genetic, and biomarker profiles that might predict treatment response.

2. The challenges of FDA approval process

There has been considerable public debate about the recent FDA approval of aducanumab for the treatment of AD under its accelerated approval program (https://www.alzforum.org/news/research-news/aducanumab-approved-treat-alzheimers-disease). This decision was based on a significant reduction of Aβ plaque in the brain and thus a surrogate endpoint thought to predict clinical benefit albeit evidence from two large phase III clinical trials (ENGAGE and EMERGE) were stopped prematurely by the sponsor Biogen because one trial failed to prove efficacy and another suggested only a positive trend toward benefits [8]. Of note, an FDA's independent medical advisory committee did not recommend approval based on the limited evidence of efficacy. In reaching its own decision under the accelerated approval pathway, the FDA has stressed that it has considered on the one hand the urgency for a serious disease with unmet medical need, on the other the anticipation of a meaningful advantage over current symptomatic therapies which is based on a disease modifying approach. The marketing authorization holder (MAH) will be required to conduct a post-approval study (phase 4 confirmatory trial) lasting up to nine years to ascertain the clinical benefit, with the caveat that if the confirmatory trials do not verify the drug's efficacy/clinical benefit, the FDA has regulatory tools in place to remove the drug from the market.

Without commenting on the merits of this case, one aspect that really interests us as regulators is the design of the post-approval trial

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including patient selection and the primary endpoint/s required by the FDA to mitigate the uncertainties in the benefits identified during the review process. Specifically, the FDA should clarify whether the phase 4 confirmatory trial will adopt a classical double-blind, placebo-controlled and parallel-group study design. The FDA should also elucidate whether future clinical trials of novel anti-AD drugs should be tested versus aducanumab or placebo. Furthermore, one should reflect on the possibility that if such confirmatory trials are negative and regulatory action is taken to withdraw this product from the market, there might be a future reluctance of the regulator to approve a medicinal product under its accelerated approval program with this level of uncertainty in its clinical benefit and evidence of efficacy based on a surrogate endpoint.

3. A EU regulatory perspective

Since November 2020, aducanumab is also under review at the European Medicines Agency (EMA) following a standard timetable for a Marketing Authorization Application (MAA) ([4], https://investors.biogen.com/news-releases/news-release-details/european-medicines-agency-accepts-biogens-aducanumab-marketing). This means that it is not under accelerated assessment and that an opinion from the EU Regulator is expected after 210 active review days excluding clock stops (3–9 months) to resolve possible concerns raised during the assessment of the application. It is not in the public domain whether applicant has requested a conditional marketing authorization (CMA) within the EU (https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation). The criteria that need to be fulfilled for a CMA within the EU are:

- a positive benefit-risk profile of the medicinal product in the claimed indication;
- the applicant will likely provide comprehensive post-authorization data within the dossier following a pre-set time-frame;
- an unmet medical need for a seriously debilitating or life-threatening disease which is justified on objective and quantifiable medical or epidemiological information;
- the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required.

During the assessment of a CMA, the Committee for Medicinal Products for Human Use (CHMP) will assess the applicant's claims about the feasibility and appropriateness of granting a CMA. Wherever the proposed post-marketing studies are deemed not feasible for the confirmation of a positive benefit-risk balance, a positive opinion might not be granted. Furthermore, with respect to the assessment of the applicant's claims on a life-threatening disease, evaluation will be relatively easy and will be based on figures of mortality and life expectancy. Justifying that a disease is seriously debilitating usually considers morbidity and its consequences on patients' day-to-day functioning and therefore for a disease to be considered seriously debilitating the EMA's guideline on CMA requires that medicinal products would need to have a major impact on patients' day-to-day functioning either already early in the course of the disease, or in the later stages [1,3].

Importantly, the EU regulator's guidance document [2] allows the possibility for the applicant to establish beneficial effects at the time of authorization potentially based on intermediate endpoints that are "reasonably likely" to translate into clinical benefit, without directly measuring the clinical benefit. In this context, applicant should demonstrate a statistically significant association between individual brain Aβ plaque reduction and a clinical benefit measure using global assessment scales, such as the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB). The guideline further elaborates that the suitability of the intermediate endpoint should be discussed in terms of the level of certainty with which the intermediate endpoint predicts clinical benefit, and why or why not any remaining uncertainties would be acceptable. In conclusion, the granting of a CMA in the EU could thus be based on an surrogate endpoint that shows that the benefits outweigh the uncertainties in the extent of the clinical benefit it translates to, and when confirmation on the clinical benefits is still required.

4. Concluding remarks

Considering the level of uncertainties, we cannot predict what will be the decision of EMA or other regulatory agencies on this application, nor how this approval will impact the upcoming regulatory landscape.

Since aducanumab's approval on the 7th June 2021, noteworthy results from two clinical studies have been published. On the 21st June 2021, results from a randomized, placebo-controlled, multi-arm trial of gantenerumab or solanezumab in participants with dominantly inherited AD (DIAD) across asymptomatic and symptomatic disease stages were disclosed. Despite both drugs demonstrated convincing Aβ target engagement, gantenerumab failed to show a beneficial effect on cognitive measures, whereas solanezumab-treated group even exhibited a greater cognitive decline on some measures compared to placebo [9]. One week later, a cross sectional study conducted on 598 amyloid-positive participants patients was published and revealed that soluble $A\beta_{42}$ levels above 800 pg/ml were correlated with normal cognition irrespective of (and despite increasing) brain amyloid burden, implying that increasing soluble $A\beta_{42}$, rather than reducing Aβ plaques, might represent a better therapeutic option [11]. We believe that these evidences should be taken into account for the future regulatory decision-making.

Another critical issue to be considered for the benefit-risk balance will possibly derive from collecting data on the potential safety concerns related to the amyloid-related imaging abnormalities of brain oedema (ARIA-E) likely associated with APOE4 carriers [10] or other rare but serious hypersensitivity reactions.

As highlighted in a recent comparative study, even though EMA and FDA have similar evaluative processes and a high rate of concordance in decisions on marketing approvals, some divergence has emerged in the past which was primarily due to differences in the interpretation of data and conclusions drawn on clinical efficacy [7]. Despite regulators worldwide formulate an opinion based on a thorough analysis of the scientific data on the benefit-risk profile of a medicinal product, we cannot rule out that this might be influenced by differences in scientific and cultural background.

Author contribution

All authors contributed equally to critical evaluation and to the whole content of the manuscript.

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Declaration of competing interest

The views expressed in this article are the personal views of the authors and may not be used or quoted as being made on behalf of, or reflecting the position of, any national competent authority, the European Medicines Agency, or one of its committees or working parties or any University.

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