Aducanumab as treatment for Alzheimer's disease: major breakthrough or improvident?

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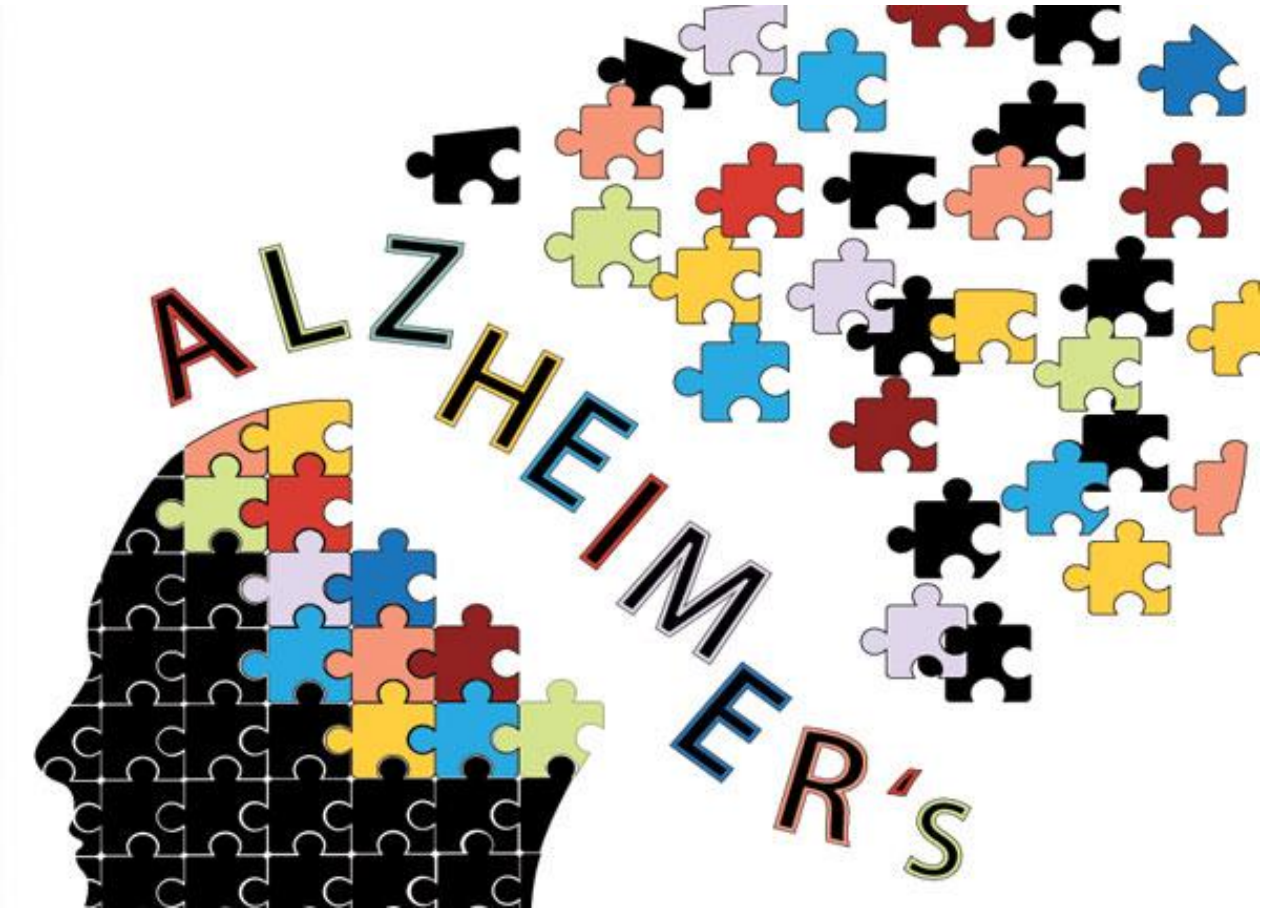

ABSTRACT

Alzheimer's Disease (AD) is characterized by the deposition of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain, leading to neurodegeneration and synaptic dysfunction. So far, antibody-based immunotherapy against Aβ deposition has been unsuccessful. A breakthrough was reached earlier this year, when the U.S. Food and Drug Administration (FDA) granted an accelerated approval to Biogen's monoclonal antibody aducanumab to be used in the treatment of AD. The decision led to a lot controversy and several members of the FDAs independent advisory panel resigned over the approval. Here the decision is investigated by looking at both preclinical and clinical studies, targeting mechanisms, adverse effects and future perspectives of several monoclonal antibodies (mAbs), including aducanumab, bapineuzumab, solanezumab, crenezumab & gantenerumab. Despite promising results on reduction of Aβ-levels after administration of different mAbs, clinical endpoints on phase III trials are yet to be found. After reanalysis of two phase III trials using aducanumab ENGAGE & EMERGE a significant benefit was reported only in EMERGE. Amyloid-related imaging abnormalities (ARIA) were not uncommon adverse effects after administration of aducanumab. Due to the failure of robust clinical evidence aducanumab has shown on the treatment in AD, the FDA approval remains highly questionable. It is arguable whether the FDA based the approval on promising results or if the incentive is mainly economical.

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INTRODUCTION

Just a few months ago, the only approved therapy for Alzheimer's disease (AD) consisted of symptomatic therapies. In mild to moderate stages cholinesterase inhibitors may be used and in a severe stage an N-methyl-d-aspartate receptor antagonist (memantine) can be administered (Adolfsson et al, 2012). These drugs provide a modest positive effect in daily activities and cognitive functions in patients, but come with several drawbacks. Firstly, they cause side effects in a substantial number of patients. Most common side effects include amyloid-related imaging abnormalities (ARIA), which can be classified in cerebral oedema (ARIA-E) and cerebral hemosiderin deposits (ARIA-H) (Sperling et al, 2011). Secondly, these symptomatic drugs do not focus on the cause of the disease, but merely on the symptoms (Kaduszkiewicz et al, 2005).
For several years, research has focussed on 'disease modifying drugs' that intervene in the neuropathological pathway of AD and may be able to counteract the progression of the disease (Ozudogru & Lippa, 2012).
A massive breakthrough in the search for a potential disease modifying drug was reached earlier this year by Biogen, an American biotechnology company specialized in neurological diseases. The U.S. Food and Drug Administration (FDA) approved the first drug for the treatment of Alzheimer's Disease (AD) since 2003: Biogen's medicine aducanumab (FDA, 2021). Aducanumab is a monoclonal antibody (mAb) which targets amyloid β (Aβ) plaques in the brain (Sevigny et al, 2016). In the last decade, several mAbs were investigated in their ability to alter the progression of AD. Two large phase III trials with bapineuzumab and solanezumab failed to yield any positive results (Prins & Schelten, 2013). Also other mAbs are not able to show any significant improvement (Dev Mehta et al, 2017). With a total number over 200 disease modifying treatments that failed or were being abandoned in the last 10 years, the approval of aducanumab is highly newsworthy (Yiannopoulou et al, 2019). However, the approval by the FDA led to a lot of controversy. An advisory committee of the FDA voted almost unanimously against authorising the drug and three members of this panel resigned over the approval (Mahase, 2021). The committee argued that, due to lack of efficacy, aducanumab should not be approved as a medicine for AD. Furthermore, not a few side effects were reported after administration of aducanumab (Padda & Parmar, 2021). Therefore, the question arises how aducanumab distinguishes itself from other mAbs, which were not able to grant an approval and didn't yield any robust results. In this essay, the history and the different trials of aducanumab will be investigated and compared with other mAbs such as bapineuzumab, solanezumab, crenezumab and gantenerumab. Furthermore, the approval itself from the FDA will be examined to see whether the incentive is mainly medical or economic.

DEVELOPMENT ALZHEIMER'S DISEASE

AD is characterized by amyloid-β plaques and neurofibrillary tangles. Amyloid-β derives from the Amyloid-β precursor protein (APP), a molecule normally involved in nervous system development, synaptogenesis, axonal growth and guidance and synaptic functions as synaptic plasticity, learning and memory

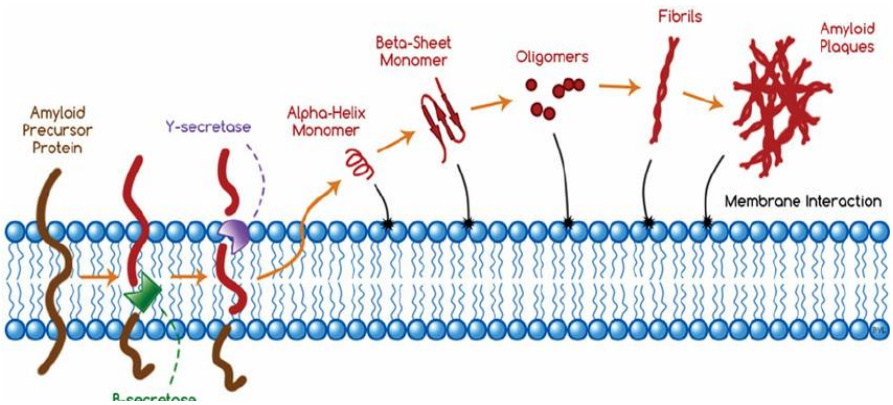

Figure 1 *Formation of amyloid-β plaques.*
This figure shows the formation of amyloid-β plaques from APP. Cleavage of APP leads to α-helix and β-helix monomers which cluster together to eventually form amyloid plaques (Drolle et al, 2014).

(Müller et al, 2017). APP is cleaved by either α-secretase or β-secretase and γ-secretase. Cleavage by β-secretase and γ-secretase forms the Aβ peptide (Figure 1), where cleavage of APP by α-secretase destroys the Aβ sequence (Numan & Small, 2000). Next, Aβ peptides can cluster together and oligomers and eventually amyloid plaques are formed which induce cell death in nerve cells (Haass & Selkoe, 2007).

Next to the Aβ plaques, neurofibrillary tangles also play an important role in the progression of AD.
These tangles arise from the hyperphosphorylation of the microtubule-associated protein tau. Under normal physiological conditions, tau stabilizes neuronal microtubules (Wang et al, 2013). Tau phosphorylation is normally well regulated by a balance between tau kinase and phosphatase activities. However, a shift in this equilibrium may result in a hyperphosphorylation of tau (Figure 2).
Tau is abnormally hyperphosphorylated in AD and is aggregated into paired helical filaments forming neurofibrillary tangles (Wang et al, 2013).

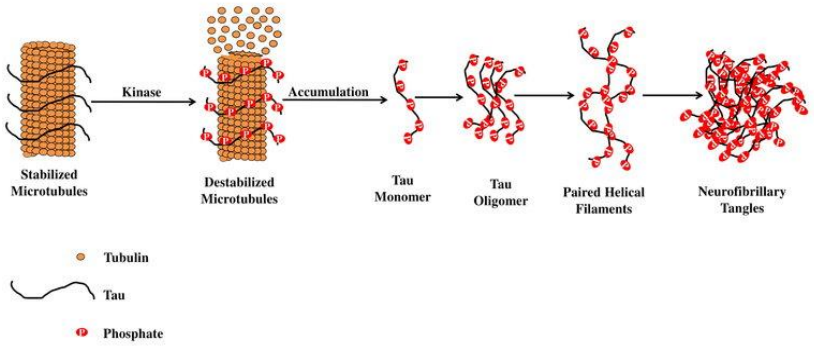

Figure 2 *Formation of neurofibrillary tangles*.
This figure illustrates the development of neurofibrillary tangles. Normally, tau stabilizes microtubules. Due to hyperphosphorylation, tau unbinds from the microtubules and eventually forms tangles via monomers, oligomers and paired helical filaments (Mamun et al, 2020).

Amyloid cascade hypothesis

Both the Aβ plaques and the neurofibrillary tangles are the most important hallmarks of the amyloid cascade hypothesis. This hypothesis postulates that the aggregation of the amyloid-β peptide in the brain is the most crucial step in the development of AD (Karren et al, 2011). As mentioned before, amyloid-β derives from the cleavage of APP by β-secretase and γ-secretase. For familial Alzheimer's Disease (FAD), some genes seem to play an important role, such as PSEN1 & PSEN 2 (Karren et al, 2011). Mutations in these genes are linked with elevated APP levels. Increases in APP can lead to higher concentrations of amyloid-β peptides. Aβ has two major isomers: Aβ40 and Aβ42. The only difference is 2 additional C-terminal residues on the Aβ42 isomer. Aβ40 levels are several times higher in cerebral spinal fluid (CSF) compared to Aβ42. Despite the abundant concentration of Aβ40 in the brain, Aβ42 is the major component in amyloid plaques (Gu & Guo, 2013). The interaction between these isoforms plays an important role in neuronal toxicity. A higher ratio of Aβ42:Aβ40 is considered an important marker for the onset of AD and a lowering of this ratio decreases Aβ

deposition in transgenic mice (Kumar et al, 2006; Kim et al, 2007). Solanezumab is known to induce plaque degradation by targeting at this equilibrium (DeMattos et al, 2001).
A shift in the Aβ42:Aβ40 and the resulting Aβ42 aggregation leads to aggregate stress, which in turn may play an important role in the paired helical filament (PHF) formation derived from the tau protein. This will lead to neuronal dysfunction and death and eventually, dementia (Figure 3).

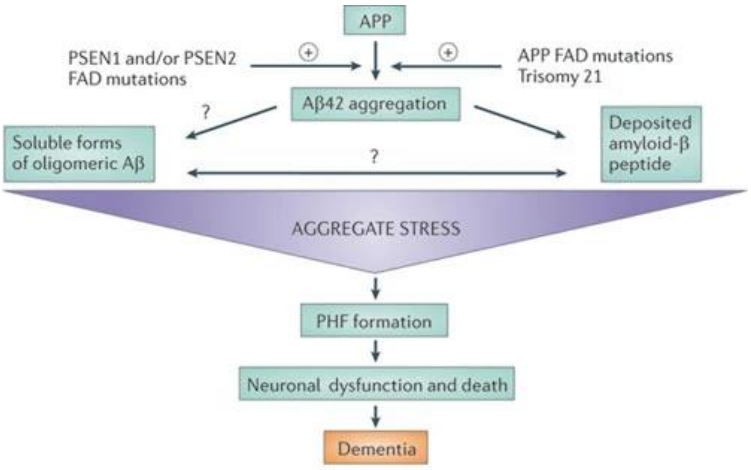

Figure 3 *Amyloid cascade hypothesis*
Elevated levels of APP, together with a shift in the Aβ42:Aβ40 ratio, lead to the deposit of amyloid-β plaques. This aggregate stress and the formation of PHFs ultimately result in neuronal loss and dementia (Karren et al, 2011).

Risk factors

Regarding amyloid-β plaques and the onset of Alzheimer's Disease, several genes are involved. Apolipoprotein E (ApoE) and presenilin-1 and -2 (PSEN) genes are well-known risk factors for the onset of AD. Isoforms and mutation of ApoE and PSEN contribute to an increased risk for developing AD, respectively.

APOE-ε

One of the risk factors of developing late-onset AD lies in the polymorphism of the ApoE gene. ApoE, an amino acid protein involved in lipid transport and cholesterol homeostasis, has three common isoforms (ε2, ε3 and ε4) which are encoded by 2 single nucleotide polymorphisms (SNPs) (Masoodi et al, 2012). Additionally, ApoE plays an important role in Aβ clearance and accumulation. Humans with at least 1 copy of the ε4 allele are thought to have a higher risk to develop AD later in life. This accounts for approximately 25% of the entire population (Correa et al, 2014). Furthermore, adverse effects after administration of mAbs is seen more frequently in ε4 carriers compared to the other isoforms. Since Aβ is continuously produced in the brain from APP, clearance of soluble Aβ is essential for preventing accumulation and aggregation. ApoE- ε4 is less efficient in soluble Aβ clearance compared to the ε2 and ε3 variants (Castellano et al, 2011). Furthermore, a study in mice showed that ABCA1 deficiency (a protein that lipidates ApoE) attenuated Aβ clearance in ε4, where no such effect was found in ε2 and ε3 (Frits et al, 2012). This indicates that both isoform and lipidation status influence amyloid-β clearance. ApoE isoforms also account for differences in Aβ accumulation, deposition and aggregation. ApoE promotes Aβ fibril formation by initiating quickening of the initial seeding or nucleation of amyloid-β peptides, where ε4 has higher aggregating abilities compared to ε3 (Yamazaki et al, 2019). ApoE ε4 also is associated with cerebral amyloid angiopathy (CAA), a pathological condition characterised by deposition of vascular amyloid in the walls of the meningeal and parenchymal arteries (Fryer et al, 2005). This will be further discussed in the 'adverse effects' section. Altogether, ApoE ε4 seems to contribute to the development of AD by promoting Aβ aggregation and reducing protective Aβ clearance, compared to the other isoforms.

PSEN1 & PSEN2

PSEN1 & PSEN2 genes encode for presenilins, which are a catabolic subunits of γ-secretase. Mutations in these genes can lead to an overproduction of amyloid-β peptides or peptides more prone to form aggregations and are the most common cause of familial Alzheimer's Disease (FAD)(, Kelleher & Shen, 2017; Lanoiselée et al, 2017). According to the amyloid cascade hypothesis,

mutations in PSEN1 initiate the onset of AD by increasing the Aβ42 production (Kelleher & Shen, 2017). PSEN2 mutations give rise to similar effects, although mutations in this gene are less frequently reported. Interestingly, PSEN2 mutations appear not only in AD patients but also in other disorders, including dementia with Lewis bodies, breast cancer, dilated cardiomyopathy and Parkinson's disease with dementia (Cai et al, 2015).

Critics amyloid cascade hypothesis

Ideally, intervention of this cascade would lead to a prevention of neuronal loss and an improvement of cognitive function. However, such evidence has yet to be found, causing a lot of controversy across the scientific field. Some opponents argue that in order to test the validity of the hypothesis, two types of test have to be performed. Firstly, the presence of amyloid-β plaques must lead to the onset of AD. In a recent review, (Ricciarelli & Fedele, 2017) state that Aβ accumulation and deposition do not correlate with cognitive decline or neuronal loss. Furthermore, it is argued that most of the knowledge available regarding Aβ pathophysiology derives from transgenic mice. Since these mice have mutations corresponding with familiar Alzheimer's Disease (FAD) and not with late onset Alzheimer's Disease (LOAD), the representation of a sufficient model is questioned (Ricciarelli & Fedele, 2017). Secondly, reduction of Aβ should cure the disease or at least ameliorate cognitive impairment. Despite aducanumab, no anti-Aβ treatments have yielded robust clinical evidence; a large number of studies failed to meet primary endpoints and several phase 3 trials were terminated early (Morris et al, 2014).

Drug development

Despite the lack of evidence supporting the hypothesis, it provides the basis of most novel drug development. When considering Aβ, there are currently three different angles regarding drug development: reducing Aβ production, facilitating Aβ clearance and preventing Aβ aggregation (Prins & Scheltens, 2013). Potential disease-modifying treatments against the Aβ plaques developed in the last years include inhibitors of the synthetic enzymes β-secretase and y-secretase, and Aβ aggregation inhibitors. A third and the most elaborated approach is immunotherapy. Both active and passive immunization are used, through vaccines and the administration of exogenous antibodies, respectively (Rygiel, 2016). These monoclonal antibodies have the advantages over vaccines of ensuring consistent antibody units and allowing control over harmful events by stopping the administration. A major drawback can be found in the fact that administration has to be repeated to preserve the desired effect (Table 1) (van Dyck, 2018).

MONOCLONAL ANTIBODIES

Aducanumab

Aducanumab (BIIB037; Biogen, Inc., Cambridge, MA) is a human Immunoglobin G1 antibody which selectively reacts with Aβ aggregates. Both soluble oligomers and insoluble fibres are targeted, but not monomers (Figure 4). Different memory B cells that react against aggregated Aβ were screened and this process discovered Aducanumab. Sevigny et al. show in preclinical studies with transgenic mice that an analogue of aducanumab crosses the blood-brain barrier and selectively targets amyloid plaques which leads to a reduction of plaques (Sevigny et al, 2016). Thereafter, a phase 1 clinical trial to test safety, tolerability, pharmokinetics and pharmacodynamics was conducted. 53 participants were included and only in the highest dose group (60mg/kg) ARIA-E was found (Ferrero et al, 2016). As a result, Biogen conducted a large phase1b trial, PRIME, which included 165 participants with prodromal or mild AD and Aβ-positive PET scans. Amyloid-β plaques reduced in a dose- and time-dependent manner, after 1 year of monthly intravenous infusions of aducanumab (1, 3, 6 or 10 mg/kg). However, the cases of ARIA-E were higher than in any previous mAb study ever conducted.

Across the 1, 3, 6 and 10mg/kg groups, ARIA-E was reported in 1(3%), 2(6%), 11(37%), and 13(41%) participants, respectively (Sevigny et al, 2016). These high numbers did not cause Biogen to stop the aducanumab trials. On the contrary, Biogen announced two large identical phase 3 trials: EMERGE and ENGAGE. 1638 and 1647 participants with a mild cognitive impairment (MCI) or mild AD were enrolled for EMERGE and ENGAGE, respectively. Patients were randomized 1:1:1 to placebo, low-dose aducanumab (3 or 6 mg/kg based on APOE ε4 carrier status)or high-dose aducanumab (10 mg/kg). Primary endpoint was change from baseline on the Clinical Dementia Rating scale Sum of Boxes (CDR-SB) (von Hehn et al, 2019). Both studies were terminated due to apparent futility. No significant benefit of aducanumab on CDR-SB was found. However, after reanalysis, the EMERGE trial revealed a significant benefit in the high-dose group (Kuller & Lopez, 2021). Instead of setting up a new experiment, Biogen (partially in cooperation with the FDA) focused on explanations why ENGAGE failed to obtain positive results. Biogen gave two possible reasons for the failure: firstly, ENGAGE showed more outliers compared to EMERGE and exclusion of these outliers made the two studies somewhat more alike. Secondly, a smaller number of patients received a high dosage of aducanumab in the ENGAGE study (Kuller & Lopez, 2021). This led to a requested Priority Review from Biogen to the FDA, which was approved earlier this year, on June 7 (see section FDA Approval) (U.S. Food & Drug Administration, 2021).

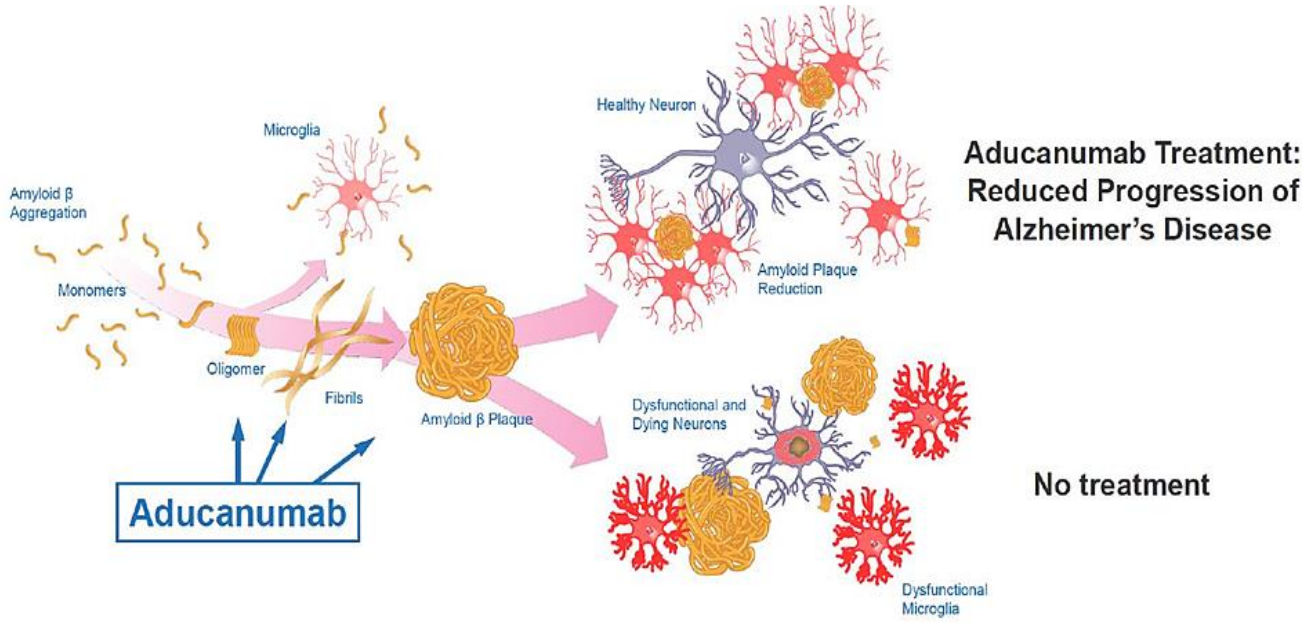

Figure 4 *Mechanism of aducanumab.* This figure shows a simplified view on the mechanism of action. Aducanumab interacts with oligomers, fibrils and Amyloid β plaques and thereby reduces the plaques (Esang & Gupta, 2021).

Bapineuzumab

Bapineuzumab (Pfizer Inc., New York, NY, and Janssen Pharmaceuticals, Inc., Raritan, NJ) is a humanized immunoglobin G1 anti Aβ mAb, which clears both fibrillar and soluble Aβ (van Dyck, 2018). Bard et al. showed that PDAPP transgenic mice (genetically altered mice which overexpress one of the disease-linked mutant forms of the human APP) administrated with 3D6 (the murine precursor of bapineuzumab) induced phagocytosis of Aβ plaques after entering the brain (Bard et al, 2000). In 2010, bapineuzumab was the first mAb to enter human testing. A phase 1 trial was conducted to determine the safety, tolerability and pharmokinetics of bapineuzumab. 30 patients with mild-to moderate AD were examined and the drug was considered generally safe and well tolerated (Black et al, 2010). However, 30% (3 of 10) of the participants in the highest dose group developed magnetic resonance imaging (MRI) abnormalities, which were in line with vasogenic oedema. As a consequence, the Alzheimer's Association Research Roundtable convened a working group to review the available trial data. A result was the fabrication of the term 'amyloid-related

imaging abnormalities' (ARIA). A subsequent phase 2 trial was conducted in which different dosages of intravenous bapineuzumab were examined. The study failed to meet the primary endpoints; no significant treatment differences were found for the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog11) and Disability Assessment for Dementia (Salloway et al, 2009).
A parallel study with a biomarker for cortical fibrillar Aβ showed some clearance of plaques. However, again several cases of ARIA were reported (Rinne et al, 2010).
A retrospective review from the phase 2 trials followed and found that 36 of the 210 (17%) patients developed ARIA-E during bapineuzumab treatment. Of these patients, 28 (78%) did not report any associated symptoms. ARIA-H co-occurred in 17 (47%) of the patients with ARIA-E. Furthermore, the presence of ARIA-E was significantly higher in APOE ε4 carriers (Sperling et al, 2012).
Two 18-months phase 3 trials consisting of 1121 APOE ε4 carriers and 1331 noncarriers studied different doses of bapineuzumab (Salloway et al, 2014). Both studies failed to meet primary endpoints (ADAS-Cog11 and Disability Assessment for Dementia). Consistent with the phase 2 trials, a greater incidence of ARIA-E in APOE ε4 carriers was reported. Thereafter, all bapineuzumab trials were discontinued in August 2012.

Solanezumab

Solanezumab (LY2062430; Eli Lilly and Company, Indianapolis, IN), a humanized immunoglobin G1, clears monomeric soluble Aβ (Zhao et al, 2017). A study in PDAPP mice found that m266 (the murine precursor of Solanezumab) reduced the burden of Aβ without binding to the deposits in the brain. Therefore, the possibility arises that Solanezumab targets the soluble form of Aβ and induces a shift in the equilibrium between Aβ40 and Aβ42 (DeMattos et al, 2001). A phase 1 and 2 trial investigated the safety, tolerability, pharmokinetics and pharmacodynamics of intravenous infusions with Solanezumab. Adverse effects like ARIA-E were far less frequent with this drug and treatment was considered generally well tolerated. Furthermore, these studies revealed dose dependent increases in CSF total Aβ (Siemers et al, 2010; Farlow et al, 2012). The phase 2 trial showed a dose-dependent increase of CSF-free Aβ42, suggesting that the shift in equilibrium makes it possible for Aβ42 to be mobilized from the plaques.
As a result, two phase 3 trials were conducted. These trials (EXPEDITION1 and EXPEDITION2) included 1012 and 1040 patients, respectively, with mild-to-moderate AD to receive placebo or Solanezumab for 18 months. ADAS-Cog14 and Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) were primary endpoints and Solanezumab failed to show significant benefit for these outcomes, but did show an excellent safety profile (incidence of ARIA-E in patients with solanezumab and placebo was 0,9% and 0,4%, respectively) (Doody et al, 2014). However, a secondary analysis of efficacy of EXPEDITION1 and EXPEDITION2 was performed solely in patients with mild-AD and demonstrated a 34% slowing of ADAS-Cog14 (Siemers et al, 2016). It is noteworthy that both studies showed a high rate of cases negative for the Aβ biomarker. Therefore, a third phase 3 trial, EXPEDITION 3, including only patients with mild-AD was conducted. To ensure positive cases for Aβ, a PET scan was required. The study included 2129 patients and showed a non-significant decline on ADAS-Cog14 (Honig et al, 2018). Due to the excellent safety profile of solanezumab two secondary prevention trials are currently in progress. Both studies are testing whether earlier intervention may result in more and significant benefit (U.S. National Library of Medicine, 2021a; U.S. National Library of Medicine , 2021b).

Gantenerumab

Gantenerumab (Hoffman-La Roche, Basel, Switzerland) is the first fully human Immunoglobin G1 and binds a conformational epitope expressed on Aβ fibrils. In PS2APP transgenic mice, gantenerumab induced reduction of plaques through microglia recruitment and prevented new plaque formation without an alteration of plasma Aβ (Bohrmann et al, 2011). A Phase 1 trial showed a dose-dependent reduction in amyloid levels and was considered generally safe. Noteworthy, the sample size was

somewhat small (n=16) and 2 out of 6 patients (33%) in the 200-mg group showed ARIA-E (Ostrowitzki et al, 2011). A phase 2 trial was started in 2010 and was expanded to a phase 2/3 registration trial 2 years later (U.S. National Library of Medicine, 2021c). Again 2 years later, in 2014, the experiment was terminated due to an interim futility analysis. The results were presented at the Alzheimer's Association International Conference and did not show any significant effects whatsoever (Lasser et al, 2015). However, post hoc analysis suggested that patients with fast progression of AD may have benefited, especially in the higher dosage groups.

Crenezumab

Crenezumab (MABT5102A; Genentech, Inc., South San Francisco, CA) binds different conformation of Aβ: monomers, oligomers and fibrils (Adolfsson et al, 2012). A phase 1 study, conducted to test the safety and tolerability, showed no cases of ARIA-E in patients with mild to moderate AD with different doses (Adolfsson et al, 2012). A subsequent phase 2 trial was started with 431 participants with mild to moderate AD. Primary endpoints were ADAS-Cog12 and CDR-SB and both outcomes failed to show significant benefit from crenezumab (Cummings et al, 2018). However, a post hoc subgroup analysis of the high dose group revealed attenuation in decline on the ADAS-Cog12 after treatment with crenezumab. This effect was only true in the mildest AD subgroup. Thereafter, a phase 3 study was started with participants with prodromal to mild AD. However, in 2019 the study was terminated for the reason that it was unlikely for crenezumab to meet primary endpoints (U.S. National Library of Medicine, 2019).

Drug	Manufacturer	IgG	Monomer recognition	Oligomer recognition	Fibril recognition	Efficacy	Trial phase	ARIA-E
Aducanumab	Biogen, Inc.	IgG1	No	Yes	Yes	One trial showed significant benefit after reanalysis	3	High
Bapineuzumab	Pfizer Inc./Janssen Pharmaceuticals, Inc.	IgG1	Yes	Yes	Yes	Failed primary endpoints	3	High
Solanezumab	Eli Lilly and Company	IgG1	Yes	No	No	Failed primary endpoints	3	Low
Gantenerumab	Hoffman-La Roche	IgG1	No	Yes	Yes	Nonsignificant benefit	2/3	Medium
Crenezumab	Genentech, Inc.	IgG4	Yes	Yes	Yes	Failed primary endpoints	2	Low

Table 1 *Specifications of different monoclonal antibodies.*

ADVERSE EFFECTS

Amyloid-related imaging abnormalities

As mentioned before, ARIA was a frequent adverse effect after treatment with several mAbs, with a higher occurrence in APOE ε4 carriers. Several studies in transgenic mice have linked APOE ε4 with cerebral amyloid angiopathy (CAA): the deposition of vascular amyloid in the walls of the meningeal and parenchymal arteries (Fryer et al, 2005). A post-mortem study in humans states that APOE ε4 is a risk factor for CAA and spontaneous ARIA-E like effects were found in patients with CAA (Greenberg et al, 1995; Kinnecom et al, 2007). The exact mechanism of ARIA is yet to be fully understood, but a hypothesis is suggested (Figure 5). Under normal physiological conditions (A) amyloid-β is cleared from the brain partly via vascular and perivascular clearance. With the progress of AD (B), this clearance is impaired due to the accumulation of vascular amyloid deposition in cerebral vessels, leading to CAA. Administration of antibodies against Aβ (C), which target the removal of Aβ from both the parenchyma and the cerebral vasculature, may cause vessels with pre-existing amyloid deposits to become more susceptible to vascular extravasation events. The degree of increased vascular permeability might depend on different factors as the severity of pre-existing CAA, efficiency of amyloid clearance and local inflammatory response. After repeated immunization (D) the risk of extravasation events should decrease due to an improvement of the perivascular clearance pathway and the vessel structure (Sperling et al, 2012).

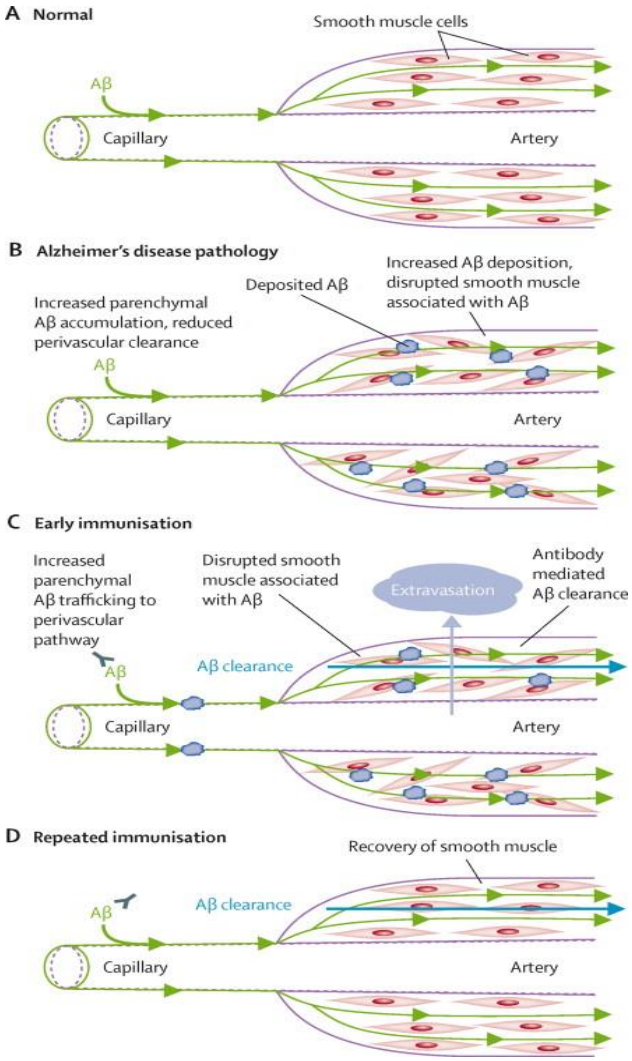

Figure 5 *mechanisms of ARIA after Aβ treatment.*
This figure shows a possible mechanism of ARIA related to CAA and treatment of monoclonal antibodies. Under normal physiological conditions (A), Aβ is cleared by vascular and perivascular clearance. As AD progresses (B), amyloid deposits can aggregate in the vessels leading to CAA. Antibody treatment can cause vascular extravasation (C) events due to higher permeability. By repeated immunization (D), these risks should be decreased (Sperling et al, 2012).

The question arises why some monoclonal antibodies induce ARIA-E (aducanumab & bapineuzumab) where others (solanezumab & crenezumab) do not show these adverse effects whatsoever. A possible explanation can be found in the inflammatory response evoked by these mAbs. Vascular extravasation has previously been linked to elevated microglial activation and their production of pro-inflammatory cytokines (Wettschureck et al, 2019). The IgG4 backbone of crenezumab shows reduced activation of Fcγ receptors (FcγR) and thereby limits FcγR-mediated inflammatory activation of microglia compared to mAbs with an IgG1 backbone (aducanumab, bapineuzumab, gantenerumab & solanezumab) (Meilandt et al, 2019). This reduced effector function may lower the risk of vascular extravasation. However, this reduced inflammatory response cannot account for the absence of ARIA-E in solanezumab, since this antibody also has an IgG1 backbone. In this case, non-appearance of cerebral oedema can be clarified by looking at the target of solanezumab, which are only amyloid monomers. Contrary to for example aducanumab & bapineuzumab, solanezumab does not target deposited plaques and thereby does not directly alter vascular amyloid levels (Carlson et al, 2016).

FDA APPROVAL

On June 7 earlier this year, the FDA approved aducanumab for the treatment of AD. The drug will be sold under the name Aduhelm by Biogen and was granted an accelerated approval. An accelerated approval is granted if the drug has an effect on a surrogate or an intermediate clinical endpoint, rather than a clinical primary endpoint. According to the FDA, "accelerated approval can be based on the drug's effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients, with a required post-approval trial to verify that the drug provides the expected clinical benefit" (U.S. Food & Drug Administration, 2021). In other words, Biogen is able to sell Aduhelm on the market (for approximately $56,000 per person per year), but has to conduct a new trial to provide evidence for the benefit of the drug on clinical endpoints (News Central Site, 2021). However, a few hours after the approval, Biogen's chief executive stated that Biogen will be given a time span up to nine years to deliver the final results and that Biogen is committed to not increasing the price for the next four years (Mahase, 2021).
Noteworthy is that, prior to FDA's decision, an Advisory Committee voted almost unanimously against the approval of aducanumab in November 2020 (10 out of 11 voted against and the 11th panel member voted "uncertain") (Biospace, 2021). This advice was ignored by the FDA, which had the consequence that three panel members resigned over the approval. Among these is Harvard professor of medicine Aaron Kesselheim, who stated that this decision was "probably the worst drug approval decision in recent US history" (Mahase, 2021).

DISCUSSION

With the accelerated approval of Aducanumab by the FDA, a major breakthrough in the treatment against Alzheimer's Disease appears to have taken place. The first approval of a medicine in almost 20 years and the very first monoclonal antibody to be approved looks exceptionally promising. The failure of several other mAbs to meet primary endpoints in phase III trials (bapineuzumab, solanezumab) seemed the end of this treatment against AD, but Biogen managed to gain an approval. Figure 6 shows a timeline of the events that in the end led to the approval.

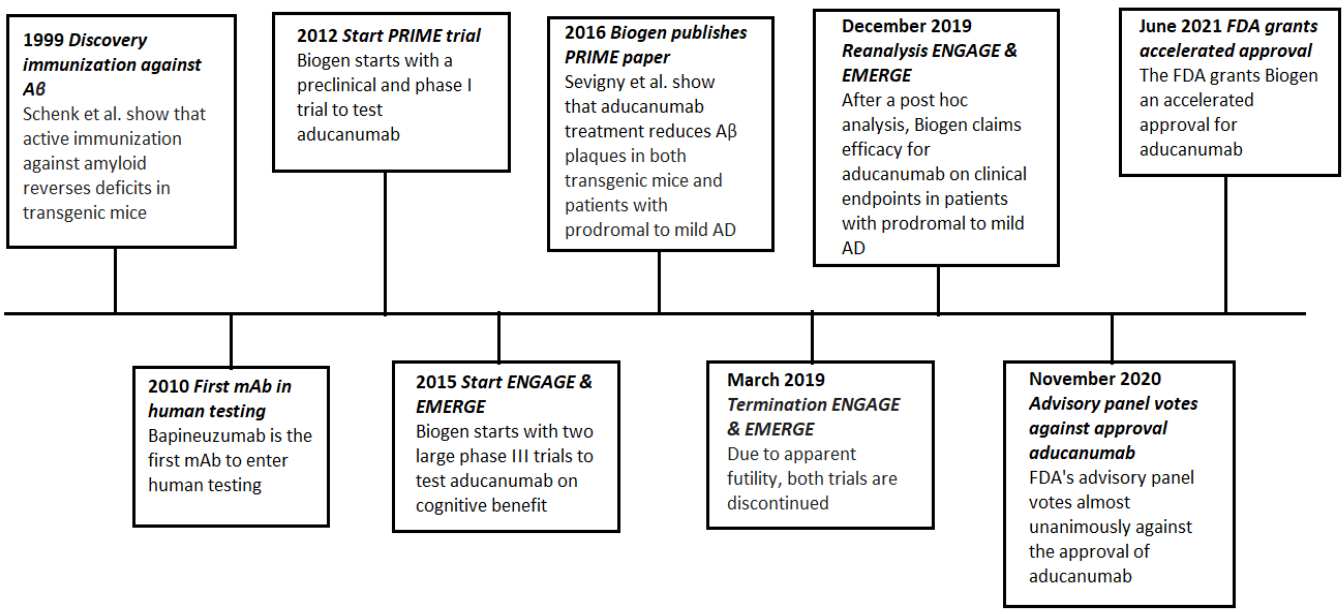

Figure 6 *Timeline of events prior to FDA approval*
This figure shows a timeline of the events that led to the accelerated approval of the FDA. Roughly 20 years after the discovery of immunization against Aβ in transgenic mice by (Schenk et al., 1999), the first mAb gained approval.

Where both phase III trials at first were terminated due to apparent futility, a post hoc analysis of EMERGE and ENGAGE ultimately led to the accelerated approval. The question arises whether this decision is justifiable or just for other incentives (economical or giving hope to patients).

First, let's look at Biogen's claim for efficacy on aducanumab. After they showed that aducanumab strongly reduced amyloid-β in a dose-dependent manner in patients with mild AD, EMERGE and ENGAGE were conducted (Sevigny et al, 2016). In March 2019, Biogen issued a press release in which they announced the termination of the trials for futility. Both trials had to demonstrate beneficial effects for aducanumab treatment, but only EMERGE trended positive and ENGAGE was not likely to meet clinical endpoints. Biogen considered this to be a failure and in a disease as AD with no good cure available and the stakes being extremely high, it seemed the correct interpretation. Next, Biogen conducted a post-hoc analysis on the two trials. Because of the promising results in preclinical trials, post hoc analysis of the phase III trials may have a beneficial effect on subsequent trials, since this analysis can be extremely helpful for the design of new experiments. However, post hoc analysis is not as strong in their predictive power as primary-specified analysis. Therefore, the FDA normally does not grant approvals based on post hoc analyses, which makes it highly peculiar that Biogen got an approval. Furthermore, it is noteworthy that post hoc analysis is not always suitable as a tool for the redesigning of subsequent experiments. In solanezumab, post hoc analysis of EXPEDITION1 & EXPEDITION2 revealed that patients with mild AD might benefit from solanezumab treatment. EXPEDITION3 was enrolled and included only patients with mild AD and failed to meet primary endpoints (Honig et al, 2018).
However, Biogen used the post hoc analysis to claim efficacy on both of the trials. Despite the identical design of the trials, ENGAGE & EMERGE differed due to variations in execution which introduced heterogeneity. Because of the concerns about high doses of aducanumab in combination with APOE ε4 carriers leading to ARIA-E, only lower doses were initially planned to be tested. However, after trial failures of lower doses of other mAbs (crenezumab, solanezumab and gantenerumab) and the assumption that ARIA-E was reversibly, Biogen decided to introduce several amendments. The most important one was the decision that APOE ε4 carriers also would be titrated with 10mg/kg aducanumab. This amendment was made over a year and a half after enrolment period and caused a shift between the two studies: more patients in the high doses EMERGE group received full possible treatment (14 doses) compared to the ENGAGE study (29% vs 22%) . This was made clear after post hoc analysis and was according to Biogen the critical variable that justified the efficacy claim on EMERGE and the failure of this efficacy in ENGAGE. The reanalysis revealed another important difference between the trials: the placebo groups performed differently across EMERGE and ENGAGE (cognitive decline of 1.74 and 1.55, respectively)(Biogen, 2019). The reason is not sure, but is most likely due to random variation that arose due to the heterogeneity of the AD biological phenotype in mildly symptomatic disease (Knopman & Jones, 2021). The larger decline of the placebo group in EMERGE is an alternative explanation for the significant benefit of aducanumab in that trial and clarifies the failure of the other. In this case, the possibility that the different outcomes of the trials are due to random variation in the placebo group cannot be excluded. Therefore, it is highly questionable that an approval mainly based on assumptions rather than robust evidence can be considered right.
When one trial yields significant benefit on clinical endpoints after reanalysis where an identical trial failed to obtain these results, one important question arises: did one trial falsely claim beneficial outcomes or did the other trial failed to obtain these results due to differences in design? At this moment, a decisive answer is yet to be given. However, considering the failed phase III trials of other mAbs (bapineuzumab & solanezumab) the former explanation looks more defensible than the latter. Before concluding an attenuation of cognitive decline after aducanumab treatment based on clinical endpoints, a follow-up phase III study is desired to confirm this statement.
Another finding highlighted by the post hoc analysis was found on biomarker level. Aducanumab reduced amyloid-β plaques in a dose-related fashion. Aβ levels remained unaltered in both placebo

groups. Most reduction was seen in both high doses groups, where a greater reduction was found in the EMERGE trial compared to ENGAGE (-.272 vs -.238 standard uptake value ratio (SUVR))(Biogen, 2019). Amyloid reduction was about a third lower in both trials in the low dose group (EMERGE -0.165, ENGAGE -.168) where the treatment was about twice as low compared to high doses. The amyloid reduction in all groups is impressive, but it is questionable if a somewhat greater reduction in plaques can cause a cognitive benefit in one group and no effect whatsoever in the other. Of course, it could be that a nonlinear effect of Aβ reduction elucidates this dose-response relationship to cognition, but that is not known yet. Further research may be needed to test whether such a relation exists. Alternatively, cognitive functioning might not be influenced by lowering Aβ which would refute the amyloid cascade hypothesis.

Furthermore, the adverse effects provoked by aducanumab should be taken into account. No other mAb showed a higher rate of ARIA: in the high doses groups of ENGAGE and EMERGE 40,3% and 41,2% of the patients suffered from these abnormalities, respectively (Biogen, 2019). This is an extremely high number, considering the statement from Biogen that only higher doses of treatment may have beneficial effects on cognitive functioning. These severe side effects should be taken extremely seriously when considering an approval, and not completely be neglected. The same can be said about the ignoring of the advisory panel. It is questionable at best to overlook an almost unanimous decision against the approval.

In sum, the decision for granting an accelerated approval is not based on robust evidence and therefore does not look deeply justifiable. A possible explanation for the approval can be found in the lack of existing medication against AD and the desire for a cure that comes with it. With progressively more rejection of the amyloid cascade hypothesis, the pressure of a breakthrough in this research field is higher than ever. However, the risk of creating false hope is rather high and it is arguable if the possibility of success outweighs this risk. A better solution may be the investigation and improvement of alternate prevention matters provided by the WHO including physical activity improvement and reducing hypertension (World Health Organization, 2019).

The timing of the approval is also undoubtedly poor, considering the pandemic the world faces at this moment. With a growing number of people questioning the reliability of the government and pharmacists, a decision based on assumption is highly undesirable.

Obviously, a breakthrough in the field of a neurodegenerative disease with a worldwide prevalence exceeding 57 million in 2019 is extremely preferable, but this does not suggest the best solution.

In conclusion, it seems that the FDA in these times of limited public trust towards research and regulations chose to support assumptions rather than clinical endpoints. The debate carriers on whilst the massive winner is Biogen.

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