Recent Treatment Approaches for Alzheimer's Disease with Monoclonal Antibodies Targeting Amyloid-β

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Abstract

Alzheimer's disease (AD) is the most common neurodegenerative disease in aging, with a complex etiology. AD is associated with amyloid-β and tau protein accumulation. Although it has been a focus of research for decades, there is no effective treatment for AD. Currently used memantine and acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine) can only slightly reduce symptoms of AD progression. These drugs are not curative and have no clear beneficial effects on the main pathological processes of the AD. In the last decade, many monoclonal antibodies targeting amyloid-β and tau proteins have been developed. Two anti-amyloid-β monoclonal antibodies, aducanumab and lecanemab, have been approved by the FDA for the treatment of AD. These breakthrough agents constitute the first disease-modifying therapies for AD that can slow the inevitable progression of AD. However, monoclonal antibodies have side effects and, patients must be carefully monitored for the occurrence of amyloid-related imaging abnormalities and infusion reactions. Despite potential harms associated with these immunotherapies, there is still hope that the early onset of AD with the administration of an accurately adjusted dose of these antibodies could provide cognitive and functional benefits.

Keywords: Alzheimer's disease, immunotherapy, amyloid-β, aducanumab, lecanemab

1. Introduction

Alzheimer's disease (AD) is a type and a common cause of dementia. It is a life-threatening medical circumstance, which is interfering with daily activities of life, functionality and lastly their vital competence by gradual worsening of neuronal capacity (Wanleenuwat et al., 2019). The AD burden increased worldwide, and it is estimated that, by 2050, there will be 152 million people with AD and other dementias (GBD 2019 Dementia Forecasting Collaborators, 2022). The prevalence rates of probable AD and dementia were reported to be 11.0% and 20.0%, respectively, in Turkey (Gurvit et al., 2008). In another study, the overall prevalence of dementia was reported to be 8.4% in Middle Anatolia, Turkey (Arslantaş et al., 2009). The prevalence is higher in women than in men across the world with the ratio 2:1 (2022 Alzheimer's disease facts and figures).

The pathogenesis contributing to poor prognosis of disease is mainly accompanied by gradual deposition of amyloid beta plaques in the extracellular region and tau-protein containing neurofibrillary tangles in the intracellular region (Chételat et al., 2012). Cognitive symptoms, neuronal loss (especially cholinergic neurons) and generalized brain atrophy are also seen in the course of disease (Khan et al., 2020; Revi, 2020). After the development of radiopharmaceuticals for amyloid beta and tau, the deposits are easily scanned by positron emission tomography (PET) scan (Valotassiou et al., 2018).

Most of the cases are manifested by memory problems, particularly the info gained recently could not be consolidated to long term memory, then causes amnesia. The perception of severity of amnesia can vary from subjective forgetfulness of patient to decreasing performance and satisfaction on different territories of life, such as work, education, social life (Fotuhi et al., 2020). The forgetfulness is a symptom which could be originated from various conditions e.g., vitamin and mineral deficiencies, hormonal disturbances, mental health disorders, social isolation, senile processes of aging, so it can be easily overlooked. The clues about current medical position of patient must be considered for all aspects (Grossberg et al., 2019). AD can also be manifested by non-memory problems at cognitive level like language, visuospatial abilities, and executive functions. For the patients above 65 years of age, dementia is usually a result of several origins rather than isolated AD. Some conditions, which contribute Alzheimer's dementia, are previous brain

infarcts, Lewy-body dementia, low nursing state, and poor nutrition (Lane et al., 2018).

Age is most relevant risk factor for AD. Throughout the history, great improvements about medical and socioeconomic circumstances are achieved and this leads to a longer life expectancy, long enough to enabling Alzheimer's dementia to appear therefore prevalence of disease escalated. Increased life quality of high-income countries leads to a decrease trend lately in incidence of disease. Thus, prophylaxis, early diagnosis and treatment takes important place to improve life quality of elderly and patients (Khan et al., 2020; Revi, 2020). Also the disease is widespread throughout the world and the symptoms are vague, it requires detailed investigation of treatment options.

AD is divided into two broad categories: sporadic and familial. Sporadic AD is the most frequent cause of dementia and accounts for more than 95% of cases. Sporadic AD tends to strike people without a family history of the disease and appears late in life, after the age of 65 (Bali et al., 2012, König and Stögmann, 2021). Sporadic cases are also called as late onset AD. On the other hand, familial AD is a rare early-onset form of AD induced by mutations in 3 major genes: amyloid precursor protein *(APP)* on the chromosome 21, presenilin 1 (PS1, encoded by *PSEN1*) on the chromosome 14, and presenilin 2 (PS2, encoded by *PSEN2*) on the chromosome 1. Mutation on these genes causes overproduction of pathological amyloid-β fragments and increased plaque formation, and directly causes early onset familial AD which give symptoms prematurely as soon as third/fourth decade. More extensively, variants of *APOE* gene, which is coding for ApoE protein, could affect the probability of occurring of disease. Variants differ from each other on the 112th or 158th amino acid. APOE2 declines the risk of disease, APOE4 enhances the risk and APOE3 stands neutral. Mutations on *MAPT* gene which codes tau protein are not related to AD but variants of genes for tau-binding proteins (BIN1, CD2AP, FERMT2, CASS4, PTK2B) are considered as risk factor owing to broad analyzes (König and Stögmann, 2021). The purpose of this review is to provide an updated information about the recent treatment approaches for AD with monoclonal antibodies targeting amyloid-β.

PubMed, Web of Science, and Google Scholar have been searched using the terms AD, monoclonal antibodies, and the name of specific agents like aducanumab, lecanemab, etc. for this review. Clinicaltrials.gov and other indexes have also been scanned for ongoing and completed or abandoned studies due to

various reasons. Anti-amyloid monoclonal antibodies, which granted approval or under investigation are evaluated according to their effectiveness, safety profile and other pharmacokinetic/clinical/imaging features. Treatment cost and patient compliance are also considered.

2. Amyloid beta peptide and tau protein

Amyloid beta (Aβ) peptide is generated through amyloidogenic pathway. Amyloid precursor protein (APP) is cleaved by β- and γ-secretases and give rise to a few products, Aβ peptide is one of them. Aβ is usually comprised 27-43 amino acids, released to extracellular space as a monomer. Depending on concentration, monomers tend to aggregate, especially 42 amino acid form. Most of the cells produce Aβ but synaptic activity leads an increase. Release into the extracellular space is greater during wakefulness. During sleep, cleared by glymphatic system on a higher level. Aβ peptide is produced and accumulated much earlier than emergence of first symptoms of disease. Eventually when the clinical symptoms are prominent, production of Aβ protein is decreased. On the other hand, tau protein is produced and concentrated simultaneously for the period of disease course. Local accumulation of tau has high predictive value for subsequent cognitive problems independent of symptoms. Relationship among Aβ, APP and tau is not precisely determined yet. Transgenic mice which hold Aβ overexpression and wild-type tau did not show any type of tauopathy or Alzheimer-like disease (van der Kant at al., 2020; Busche and Hyman, 2020).

3. Diagnosis of AD

Guidelines for AD diagnosis are revised in 2011 and mentioned three stages of disease (Yaari et al., 2011).

1. *Preclinical:* Amyloid and tau accumulations are seen, but any clinical symptom or sign is absent.
2. *Mild cognitive impairment* (MCI)*:* Memory problems or other weakening on the cognitive abilities does exist, and these deteriorations are not correlated with patient's age or education considering a healthy individual. Nevertheless, there is no severe symptom which impedes patient's independence. MCI could or could not lead to AD.
3. *Dementia due to* AD*:* Last stage of disease, clinically evident symptoms (memory loss, difficulty in finding words, visuospatial problems) are present. Patient cannot maintain their life independently.

PET-scan is beneficial for staging of disease, prediction of prognosis for short term and diagnosis of disease. Aβ-PET scan

could be carried out via FDA and EMA approved indicators, such as florbetapir (FDA approval: 2012), flutemetamol (2013) and florbetaben (2014) (Chételat et al., 2020). PET-scan using these agents is useful to show the distribution and intensity of Aβ even before the onset of disease, but is insufficient for electing between AD subtypes or clinical phenotypes. ^{18}F-flortaucipir is another agent for PET-scan, helpful for tau protein (Bao et al., 2021; Tian et al., 2022).

There are also some cerebrospinal fluid (CSF) indicators are present. Amyloid beta 42 ($A\beta_{42}$) refers to 42 amino acid consisting form of amyloid beta protein. This kind of Aβ is more prone to aggregate as neurotoxic $A\beta_{42}$ oligomers. Level of $A\beta_{42}$ monomers in the CSF is decreased at the symptomatic and initially asymptomatic patient group due to oligomerization. P-tau181 refers to phosphorylated tau protein at 181st amino acid. This protein is specific for tauopathy but total tau (t-tau) amount in CSF is a general indicator for neurodegeneration. Despite both p-tau181 and t-tau levels are elevated in MCI or dementia due to AD, none of them is used for settling severity or staging of disease. P-tau217 is thought to be more specific than p-tau181, but not clinically used yet (Knopman et al., 2021). Some other indicators in CSF (neurogranin, SNAP25, synaptotagmin 1) are currently being investigated, but specificity for AD has not been determined yet (Tan et al., 2014).

4. Prevention and Treatment of AD

Presently, no proper medicinal treatment is available for AD that inhibits or slows neuronal destruction, and prevent disease. However, lifestyle changes on modifiable modalities like exercise and cognitive stimulation are accepted to postpone clinically overt cognitive deterioration (Khan et al., 2020; Revi, 2020; Knopman et al., 2021).

Traditional pharmacological treatment:

1- Cholinestherase inhibitors: Rivastigmine, galantamine, donepezil

2- N-methyl-D-aspartate (NMDA, Glutamate) receptor antagonist: Memantine

Acetylcholine (ACh) is a crucial excitatory neurotransmitter for memory, learning, and other cognitive abilities. In the AD, cholinergic neurons are destroyed and thus, ACh level is decreased on the synaptic cleft. Cholinesterase inhibitors suppress cleavage of ACh on the synaptic cleft. Increased ACh levels cause better intercellular interaction, therefore dementia symptoms are decelerated or stabilized (Sharma, 2019; Haake et al., 2020). Galantamine and rivastigmine are approved for mild to moderate level AD in the USA

and European countries. Donepezil is approved for severe AD. Cholinesterase inhibitors delay symptoms about 6 months. Adverse effects includes nausea, vomiting, diarrhea, loss of appetite. Memantine is the first agent approved for moderate to severe AD in 2003. Extrasynaptic NMDA receptors which are continuously stimulated contributes neurotoxicity through unceasing calcium flow upon the channel on the receptor (Folch et al., 2018). Memantine targets to inhibit this stimulation and protect neurons by preventing neurotoxicity due to overstimulation (Majidazar et al., 2022). Memantine and the acetylcholinesterase inhibitors are unable to affect AD progression. They are not curative, and used only for partial symptomatic relief (Olivares et al., 2012). Since traditional agents cannot reverse the disease course, it should be studied more precisely on the mechanism of formation of disease. As the accumulation begins years before the manifestation of clinical symptoms, monoclonal antibodies targeting Aβ accumulations plays a very important role in the mechanism of disease.

5. Anti-amyloid monoclonal antibodies

Anti-amyloid monoclonal antibodies are the first disease-modifying therapies for AD and these breakthrough agents can slow down the inevitable progression of AD into more severe cognitive impairment. Neurobiological basis and symptoms, bio-indicators and amyloid related imaging abnormalities seen in the AD are intended to be reversed by using monoclonal antibodies (Dhillon, 2021). Although many clinical trials directed at Aβ have failed to demonstrate a significant effect on clinical benefit, recent studies with monoclonal antibodies redefine the treatment of patients with AD and introduce a new era in AD therapy (Cummings, 2023). Anti-Aβ antibodies may directly bind to Aβ and either dissolve Aβ aggregates or prevent Aβ oligomerization and fibril formation (Fu et al., 2010). Targets of monoclonal anti-Aβ agents on different aggregation forms of Aβ are shown in Figure 1.

5.1. Aducanumab (BIIB037)

Aducanumab is a human immunoglobulin G1 produced for soluble and unsoluble forms of aggregated Aβ. In June 2021, aducanumab gained accelerated approval from FDA, and is the first antibody on this field (Dhillon, 2021).

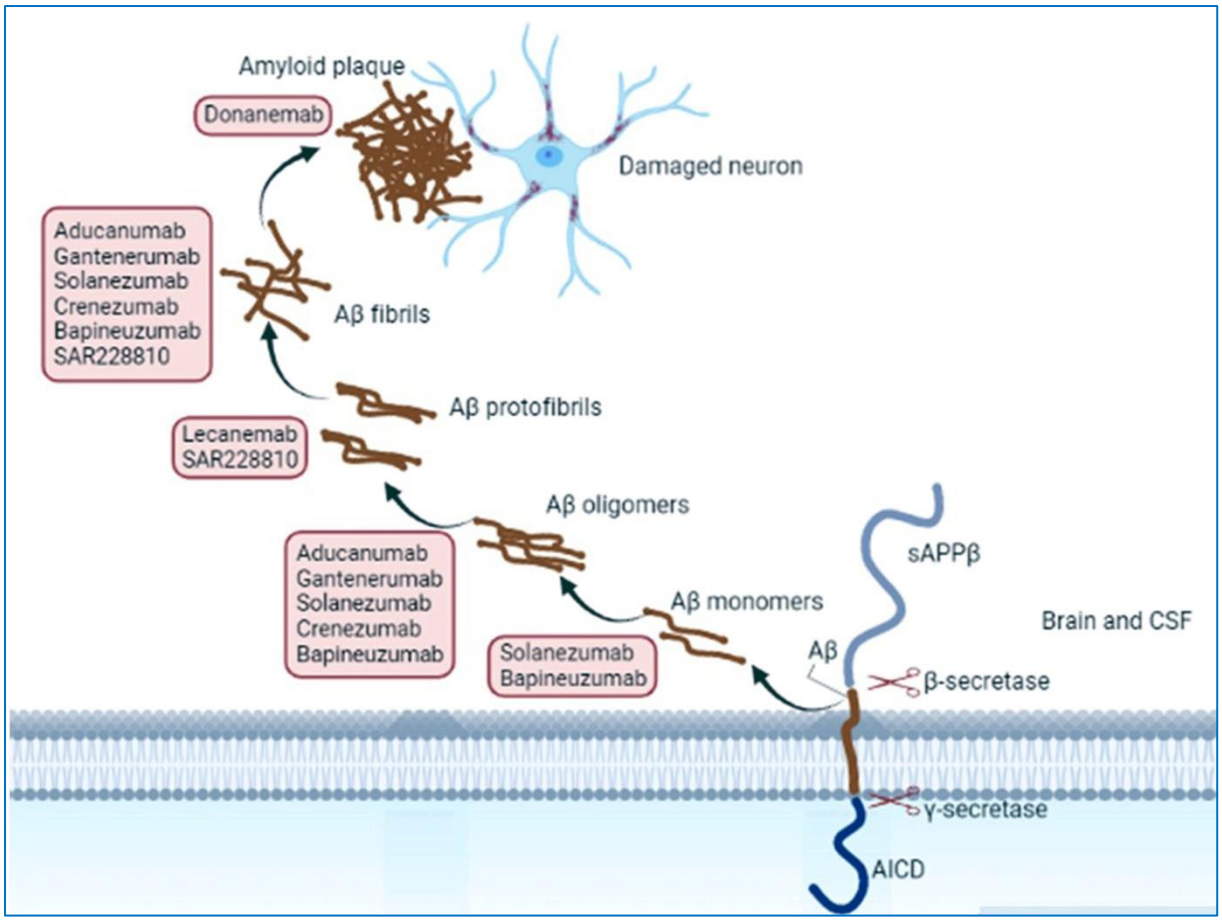

Figure 1. Targets of monoclonal anti-Aβ agents on different aggregation forms of Aβ. Aβ, amyloid beta; AICD, amyloid precursor protein intracellular domain; CSF, cerebrospinal fluid; sAPPβ, soluble amyloid precursor protein-β. This illustration was created using BioRender.com.

Accelerated approval term has been used for the first time on a neurological disease with the approval of aducanumab (Dhillon, 2021). Aducanumab does not bind Aβ monomers, but binds to fibrils and transforms them as a target for microglia mediated cleaning. So, the bridge between neuroprotective Aβ monomers and neurotoxic Aβ oligomers is interrupted and aggregates are more prone to be cleansed (Fu et al., 2010; Haddad et al., 2022). Maximal benefit is reached on the 5th month of therapy. A study includes 165 subjects that are prodromal or mild AD patients and applied different intravenous doses of aducanumab; cortical amyloid accumulation is decreased enormously. The accelerated approval of aducanumab was based upon significant Aβ plaque diminution as measured by amyloid PET. ENGAGE and EMERGE studies; are most known phase 3 trials for aducanumab, both started on September 2015. In the EMERGE trial, high dose aducanumab is

applied to subjects and 22% of them shown decreased cognitive decline. In the ENGAGE trial, cognitive decline did not stop, and the manufacturer is required to confirm the benefits of the drug in the phase 4 study (Budd Haeberlein et al., 2022). The drug is approved for all stages of disease, although it is studied for mild subjects on the phase trials. For the safety and effectiveness concerns, literature still lacking adequate data. While prescribing, patients on the level of mild dementia or mild AD are most appropriate group for the treatment. Most common adverse effects are including headache and diarrhea. Risk for cerebral edema is increased, but there is no subject died in the experimental process. Aducanumab has not been approved by the European Medicines Agency (EMA) due to inconsistent effect, lack of clinical correlation, and potentially severe side effects. Aducanumab is administered as monthly infusions, which takes 1-3 hours, and the cost was initially estimated to be $56,000 per year. Remarkably, because of low sales, the costs have been decreased in December 2021 to $28,200 per year (Brockmann et al., 2023).

5.2. Lecanemab-irmb (BAN2401)

Lecanemab is a humanized mouse monoclonal antibody (immunoglobulin G1), and was granted accelerated approval by the FDA on 6 January 2023. FDA converted lecanemab to traditional approval (on 6 July 2023) following a determination that a confirmatory trial verified clinical benefit through Clarity AD study (Cohen et al., 2023). Lecanemab binds to soluble Aβ aggregates, which are protofibrils, an intermediate step in amyloid plaque formation (Villain et al., 2022). Phase 2 trial took 18 months, and five different doses (2.5 mg/kg biweekly, 5 mg/kg biweekly, 5 mg/kg monthly, 10 mg/kg monthly, 10 mg/kg biweekly) and placebo are performed. Among these doses, biweekly 10 mg/kg intravenous infusion dose is considered as effective dose 90 (ED_{90}) (McDade et al., 2022). On the March 2019, phase 3 trial named as CLARITY AD has started for 18 months and continued 2 years as open label. Results of phase 3 trial are supported by increased Aβ monomers and decreased p-tau181 levels in the CSF (Swanson et al., 2021). The manufacturer also investigates the delaying effect of agent on the cognitive symptoms of asymptomatic risk group patients in the AHEAD 3-45 trial (Rafii et al., 2023). Lecanemab has demonstrated significant amyloid reduction on amyloid PET and showing of clinical benefit in clinical trials (Rofo et al., 2021; Swanson et al., 2021; van Dyck et al., 2023). Lecanemab is generally well tolerated, removes Aβ aggregates quickly than aducanumab with a lower rate of adverse effects. As an adverse effect,

amyloid related imaging abnormalities are 12.4% for therapy group and 5.7% for placebo group (van Dyck et al., 2023). Lecanemab costs US $26,500 per year (Brockmann et al., 2023).

5.3. Gantenerumab (RO4909832, RG1450)

Gantenerumab, a fully human immunoglobulin G1 antibody, is able to bind two discontiguous regions of Aβ, with highest affinity at residues 2-11 and 18-27. In the two studies of phase 2 and 3 for gantenerumab (SCarlet RoAD phase 2/3, Marguerite RoAD phase 3) monthly 105 and 225 mg doses of subcutaneous treatment is applied to subjects. These studies are concluded because the early outcomes are not reached. Then, these studies became open label and patients are given 1200 mg gantenerumab monthly. On the latter design, meaningful amyloid plaque decrease is achieved but one third of patients survived cerebral edema (Ostrowitzki et al., 2017; Klein et al., 2019). Gantenerumab has studied on the early symptomatic autosomal dominant AD patients and negative results for therapy has reached. A phase 3 randomized trial of gantenerumab in prodromal AD was stopped early after a futility analysis (Ostrowitzki et al., 2017). In October 2021, gantenerumab has gained fast track approval status. In February 2022, due to Centers for Medicare and Medicaid (CMS) notes, manufacturer decided to not to apply FDA until the end of phase 3 trials (Bateman et al. 2022). On a different trial named BRAINSHUTTLE AD, a form of gantenerumab is studied. This form is easily passed through blood-brain barrier, includes a fragment bound to effector part of gantenerumab and binds transferrin receptor (Cummings et al. 2023). Another phase 3 trial named SKYLINE, effect of gantenerumab on the asymptomatic subjects under AD risk is investigated about revealing cognitive symptoms. It differs from other agents by the route of administration, gantenerumab is administrated subcutaneously while other monoclonal agents are administrated intravenously (Cummings et al. 2023).

5.4. Donanemab (LY-3002813, N3pG)

Donanemab is a humanized IgG1 antibody originated from the murine immunoglobulin G2a antibody mE8. It recognizes and binds to the pyroglutamate form of Aβ, which aggregates in the amyloid plaques (Rashad et al., 2022). As it is a plaque specific antibody, binds to Aβ3-42. Donanemab shows a remarkably high Aβ clearance (Villain et al., 2022). In a study compared to aducanumab, on the early phase symptomatic patients, the brain amyloid plaque levels are decreased 65.2% with 6 months of treatment. However,

donanemab alone is strongly immunogenic. While the other monoclonal antibodies are contraindicated for coagulopathies and anticoagulant use, donanemab is safe for these groups of patients. After the complete response letter from FDA for fast track approval in 19 January 2023, the manufacturer (Eli Lilly) served the phase 3 study (TRAILBLAZER-ALZ 2) results for donanemab in 3 May 2023. Donanemab has significantly reduce the pace of cognitive decline and other areas for the early phase of symptomatic Alzheimer's patients (Lilly News Release, 2023). It is thought to have the price of $71.600 annually.

5.5. Bapineuzumab (AAB-001; Bapineuzumab-modified, AAB-003)

Bapineuzumab is a humanized monoclonal IgG1 antibody that targets Aβ1–5 (N-terminal residues). Bapineuzumab-modified, is an analogue of Babineuzumab with diminished Fc-receptor-mediated effector function, AAB-003, which is expected to have a better safety profile (Delnomdedieu et al. 2016). Phase II clinical trials showed that there are falls in CSF p-tau and t-tau levels (Blennow et al., 2012). However, another clinical study demonstrated that no marked difference was observed in functional and cognitive decline between early and delayed treatment groups (Salloway et al., 2018). Additionally, amyloid-related imaging abnormalities with edema or effusion incidence was higher in cases first exposed to bapineuzumab group (Salloway et al., 2018). Recent meta-analysis showed that bapineuzumab is safe in the treatment of AD patients, but vasogenic edema should be considered (Gao et al., 2023). Bapineuzumab can improve function and cognition, as well as activities of daily life in mild or moderate AD, and meanwhile, it can induce serious adverse events (Hao et al., 2023).

5.6. Solanezumab (LY2062430)

Solanezumab is a monoclonal antibody which binds to a mid-domain epitope of the Aβ peptide (amino acid residues 13–28). Phase 3 trials of solanezumab (EXPEDITION 1 and EXPEDITION 2) for mild-to-moderate AD showed that the agent failed to improve cognition or functional ability (Doody et al., 2014). The EXPEDITION 3 trial of solanezumab in cases with mild AD was discontinued early due to ineffectiveness (Doggrell, 2018). A recent meta-analysis showed that low-dose solanezumab (400 mg every 4 weeks for 80 weeks) slows clinical progression of AD with mild dementia (Holdridge et al., 2023).

5.7. Crenezumab (MABT5102A, RG7412)

Crenezumab is a humanized monoclonal immunoglobulin G4 antibody targeting β-amyloid oligomers. CREAD

and CREAD2 phase 3 studies showed that no meaningful modifications in AD biomarkers were detected. Both studies were terminated following a preplanned interim analysis showing that crenezumab was well tolerated, but did not inhibit clinical decline in participants with early AD (Ostrowitzki et al., 2022).

5.8. Ponezumab (PF04360365, RN-1219)

Ponezumab is a humanized IgG2δA antibody that has two mutations (A33S and P331S) to minimize potential immune effector function. Like solanezumab, it is hypothesized to deplete brain Aβ stores by sequestering Aβ in the blood and thus shifting the brain-blood equilibrium. Although ponezumab generated a favorable safety profile, two subsequent phase 2 studies showed no marked clinical benefit for treatment of mild-to-moderate AD, and further ponezumab studies were discontinued (Landen et al., 2017a, 2017b). In another phase 2 study evaluating the effects of ponezumab on potential cerebral amyloid angiopathy, no statistically significant difference was found between ponezumab and the control group. It was observed that cerebrovascular reactivity measured by blood oxygenation level dependent functional magnetic resonance imaging shows a decrease trend. Nevertheless, the number of new microbleeds was the same in both groups despite ponezumab treatment (Leurent et al., 2019).

5.9. SAR228810

SAR228810 is a humanized monoclonal immunoglobulin G4 antibody with limited Fc effector functions that binds specifically to soluble protofibrils and insoluble fibrils of Aβ (Pradier et al., 2018). Although SAR228810 was found to be well-tolerated, an upper limiting dose as defined by adverse events was not reached in phase I clinical trials (NCT01485302) of 44 single-dose and 48 multiple-dose patients, no additional trials have been scheduled to date.

6. Conclusion

Until now, the nine agents under investigation or approved have been discussed. Among these, only two of them are human immunoglobulin (aducanumab and gantenerumab) and the rest are humanized immunoglobulin. Between human immunoglobulins, aducanumab binds both soluble and nonsoluble forms of aggregated Aß on one site, but gantenerumab binds two different sites of Aß. Additionally, gantenerumab has a form, which passes blood-brain barrier through transferrin receptor. Aducanumab binds already formed and aggregated forms of Aß but lecanemab binds protofibrils, thus prevents the progression of aggregation.

Aducanumab, lecanemab, gantenerumab, donanemab and bapineuzumab resembles immunoglobuline G1 (others are not) and have found to be clinically effective on the cognitive decline and reversed it. Crenezumab, ponezumab and SAR228810 do not have that kind of consequence yet. Solanezumab has considered ineffective but then found to be effective at consistent low doses. Still, it takes long to exert its effect. Gantenerumab is the one, which is subcutaneously administered. Others are administered by intravenous infusion. Donanemab is plaque specific but it maintains its strongly immunogenic effect, which makes it difficult to adapt clinical practice. Similarly, bapineuzumab alters levels of indicator proteins in CSF, but causes vasogenic edema.

Currently, there is no radical therapy for AD, and many pharmacological strategies are evaluated to delay the progression of cognitive impairment and memory loss. Thus, it is crucial to discover novel therapeutic targets. Monoclonal antibodies targeting amyloid-β are able to cause plaque elimination and may improve cognition. Anti-amyloid monoclonal antibodies reduce the rate of decline in AD by about 30%. However, current monoclonal antibodies have important limitations. They give rise to unwanted outcomes about adverse effects and immunotherapy. The disadvantages of immunotherapy are the need for repeated injections, high costs, the risk of hemorrhages, edema formation, and the induction of an immune response to the injected antibodies. Successful advancements in Aβ-directed immunotherapy with the development of safe and effective antibodies may revolutionize the treatment of AD.

For further studies, the purpose must be agents that are more suitable for both patient and practitioner. Infusion and subcutaneous injection are painful administration routes for patients. Oral or transdermal forms could be more acceptable for patient. Treatment is generally planned to be achieved in a healthcare institution, maybe focusing auto-administration of drug by patient himself at home could be an easier way and decrease overall healthcare costs.

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