Alzheimer's Disease: A Systemic Review of Recent Substantial Amyloid Beta Disaggregation Therapeutics

Ritik Manyania[1] andManpreetKaur Aulakh[2]

[1,2]*Department of Chemistry,Chandigarh University, Gharuan-140413, Mohali, Punjab, India*

E-mail:[1]*ritikmanyania01@gmail.com*

[2]*manpreet.e12119@cumail.in*

Abstract

Alzheimer's disease (AD) is a debilitating neurodegenerative disorder associated with impaired cortical as well as cognitive functions.One of the causes of AD is the accumulation of beta-amyloid (Aβ) plaques outside and surrounding the nerve cell. The accumulation of Aβ peptides inside the neurons involves in cognitive impairment, synaptic dysfunction and constitution of amyloid plaques. Aβ aggregation is believed to play a critical role in the pathogenesis of AD. As a result, therapeutics aimed at disrupting or reversing Aβ aggregation have garnered significant attention in recent years.Still no effective treatment has been made which can slow down the progression of these Aβ plaques. Based on various researches, different anti-Aβ drugs have been made to decrease the production of Aβ plaques by inhibiting the β and γ-secretase enzymes and also to stimulate the breakdown of preexisting Aβ plaques in the brain. Globally, many drug companies have performed clinical trials on AD patients, based upon amyloid hypothesis, to synthesize anti-amyloid drugs. Many researchers have dismissed the Aβ hypothesis of AD due to the failure of several amyloid-targeted therapies in various clinical trials performed on AD patients, as discussed in this article. Researchers are still developing and testing various therapies for an ideal drug of AD, in ongoing clinical trials. In this article, such anti-amyloid drugs are discussed which can prevent the formation of Aβ oligomer and suppress their toxicity.

Keywords: Alzheimer's disease; β-amyloid; Amyloid cascade hypothesis; APOE4 genotype; Anti-amyloid antibodies; β-secretase inhibitors

1. Introduction

The most widespread type of dementia is Alzheimer's disease (AD), a terminology refers to loss of memory and other cognitive deficits that are severe enough to cause difficulty in daily activities, causing patients and their families enormous suffering. About 50 million people are currently suffering from AD worldwide. After cardiovascular and cerebrovascular disorders and malignant tumors, AD has risen to become the third most frequent factor causing disability and death amongolder individuals[1].AD is a neurological disorderresults in memory loss and cognitive impairment[2].Dementia is a disorder marked byprogressive decrease in more than two cognitive domains, like memory, language,visuospatial function,behavior, and personality as a result of which the ability to execute essential everyday activities are lost[3]. The World Health Organization (WHO) has classified AD as a global public health issue.No specific medication has been found for this illness as of yet [4].

Alois Alzheimer hospitalized a 51-year-old patient named Auguste D., for growingcognitive impairment about a century ago. After some years of her death, Alzheimer's histological tests of her brain lead him to the conclusion that he was witnessing a distinct clinical-chronic process, which was later termed AD[5].AD is a complex disorder with several facets that are influenced by multiple factors. Because the human brain is so complicated, it is still unclear exactly how AD pathophysiology works.Many different hypotheses, including the Aβcascade hypothesis, cholinergic, tau, presenilin, oxidative stress, calcium inflammatory hypothesis, and others, have been put forth for AD. As a result, several efforts have been made to create anti-AD drugs based on these concepts[6].

At microscopic level, it is studied that the characteristic nodules in AD were also extracellular senile plaques, formed by Aβ peptide reserves, and intraneuronal fibrillary clumps formed by abnormally hyperphosphorylatedtau protein in thecortex and medial temporal lobe structures of brain. The mechanism responsible for causing AD is still not entirely known, but hereditary, pathological, and metabolic evidence suggests that gradual manufacturing and subsequent growth of Aβ, a proteolytic subunit of the membrane-associated amyloid precursor protein (APP),plays a very important role.The main component of neuritic plaque, Aβpeptide, is produced in excessive amounts by abnormal breakdown of APP, a membrane-bound glycoprotein with a primary function that has not yet been determined but has been connected to neuronal plasticity and the establishment of neuron synapse [7].The primary physiological pathway of APP digestion in neurons is followed out by α-secretase and γ-secretase to form P3 protein.However, in AD, an amyloid precursor protein pathway is promoted by the breakdown of APP by β-secretase, accompanied by γ-secretase, to form Aβ peptides comprising 39 to 42 amino acid residues. According to biochemical investigations on cell lysates as well as brains, the most prevalent are Aβ 1-40 (90%) and Aβ 1- 42 (10%). Cells in the brain secrete this protein in a dissolved form, which is normally eliminated. However, when aberrant conditions make more APP susceptible to β-secretase cleavage, the Aβ elimination mechanism in the process becomes overwhelmed. This ultimately results in the accumulation of Aβ, which forms oligomeric, multimeric, and fibrillar clumps, causing neurodegeneration. The aggregation as well as deposition of Aβ results in the production of extracellular plaques, which are one of the physiological markers of the illness[8].

2. Amyloid Precursor Protein (APP) and β-amyloid Production

Initially, amyloid proteinwas isolated and distinguished from the AD patient's cerebral vasculature of brain and thereafter the cloning of APP was done [9].The cleavage of APP is done with the help of secretases enzyme, as it is a type-I transmembrane protein. The APP gene can be found on chromosome 21 and three major isoforms (or homologs) can be prepared from its mRNA by the process of alternative splicing. Amino acid homologuei.e. 695mainly found in neurons, preferentially 751 and 770 homologue amino acidssystematically expressed. TheAβ region in the APP is found partly inside theectodomain and transmembrane region of APP as the peptides of 40-43 amino acid residues. Aβ42 is the disease-associated isoform of Aβ, accounting for 5-10% total amount of Aβgenerated[10].The amyloid plaques which are deposited initially seen in thebrains, suffering from AD, are generated due to Aβ42. APP is processed by proteolysis by enzymesα, β, and γ-secretases. At amino acid 17, α-secretase enzyme cleaves the majority of

APP in the Aβ domain, which results in the non-generation of Aβ, and it generates soluble αAPP which subsequently released in non-amyloidogenic pathway.APP, on the other hand, isalso cleaved by β-secretases and γ-secretasesin the Aβ domain at the N-terminus and C-terminus respectively, which results in the generation of Aβ in amyloidogenicmechanism[11].A larger amount of APP is present in patients suffering with Down syndromedue to the trisomy of chromosome 21. The AD is generally known to grow too soon in peoplesuffering with Down syndrome[12].In addition, automatic transmission dominant mutations of APP and presenilin associated with contagious forms of premature AD have been demonstrated to increase Aβoutput and to generate more Aβ aggregation. So Aβ peptide has become centralfocus to AD research on the basis of these genetic markers. Aβ was originallycreated at the plasma membrane and supposed to be released in the extracellular form ofAβ. It is postulated that in AD patients, released Aβ progressively accumulates in extracellular environment till it begins the formation of clumps of β-pleated amyloidfibrils which are insoluble in nature and are made up of 7-9 nm broad antiparallel-pleated sheets of fibres. Several theories suggeststhat these extracellular Aβ fibrils have a detrimental impact on the neighboring nerve cells and their functions[13].Recently, it has been proposed that intermediary products of Aβ fibril synthesis, such as Aβ oligomers having lower molecular weight and protofibrils, are extremely harmful to neurons and alter neuroplasticity than Aβ fibrils[14].Furthermore, soluble Aβinteractsmore with brain functions in the AD brain than insoluble Aβ .Protofibrilsis a soluble form of Aβ and these soluble Aβgroups aregenerally assumed to have significantpathogenic impacts[15].

3.Aβ Cascade Hypothesis

The transmembrane protein APP, which is a component of many cell types, including neurons and glial cells, is broken down into peptide Aβ during the proteolysis process. There are several versions of the molecule produced by substitution concatenation in humans, with APP695 being the most prevalent [16][17][18]. The enzyme protein complex -α, -β, and -γsecretase, which is made up of presenilin and nicastrin molecules, cleaves APP into smaller peptide pieces, one of which is Aβ.When APP is catabolized by α-secretase, two fragments are produced: a soluble sAPPα fragment that stays in the extracellular space andan 83 carboxyterminal amino acid fragment (C83) that is attached to the plasma membrane [19][20][21]. In addition to improving synaptic plasticity, learning, and memory, sAPPα also helps to reduce metabolic stress and regulate neural excitability.APP is selectively cleaved by β-secretase 1 (BACE) in neuropathic conditions, resulting in the fragmentation of APP into sAPPβ and a fraction of 99 amino acids (C99). The peptides Aβ(1-40) and Aβ(1-42), which are produced after further processing of C99 cleavage by γ-secretase, are believed to be responsible for the development of neuritic plaques [22].The pathophysiology of AD, which results in neurotoxicity and neuronal degeneration, is heavily influenced by the production, aggregation, and deposition of Aβ peptides, particularly Aβ(1-42). This is supported by amyloid cascade hypothesis[23]. The development of fibrillar plexuses and enhanced Tau phosphorylation are two additional effects of excessive extracellular Aβ. The amyloid cascade hypothesis, however, falls short in describing the fundamental reasons of rare AD, where formation of Aβ is unlikely to have a clear hereditary basis [24][25].

3.1.Antiamyloidogenic Pathways as Potential Therapeutic Targets for Modifying the Progression of AD

The pharmaceutical industry has mostly concentrated on amyloid-centric approaches during the past 20 years, investing significant resources to create effective AD medicines. Experts have questioned the strategy's practicality, nevertheless, in light of the numerous clinical trial failures of drug candidates [21][22][25].One potential reason for failure is the absence of biomarkers that can precisely detect AD in its initial stages. The people who are currently being enrolled in phase III studies appear to be suffering from advanced stages of AD, rendering any suggested treatment ineffective. New diagnostic tools which are able to do early detection are therefore critically needed. Meanwhile, numerous new medications that target the mechanism of amyloid production are continually being developed. The inhibition of γ- and β-secretase can lower the Aβ production from APP, and increasing α-secretase activity must be taken into account [26].

3.1.1. β-Secretase Inhibitors and its Modulators

The amyloidogenic APP-processing pathway's early stages involve the β-secretase enzyme complex. Because this complex also includes multiple additional substrates in addition to the APP, it is challenging to make β-secretase inhibitors.For instance, β-secretase's ultimate target is neuregulin-1, which is crucial for CNS axon myelination and synaptic plasticity [18].Even if the enzyme is specifically inhibited, a wide range of substrates might cause considerable adverse effects.Nonetheless,MK8931 (clinical trial ID# NCT01739348),E2609 (NCT01600859),and LY2886721 (NCT01807026 and NCT01561430) have all showneffectiveness in lessening Aβ production in the cerebrospinal fluid (CSF) by up to 80–90% in people. So yet, no β-secretase inhibitors have reached the market[27][28][29][30].

3.1.2.Inhibitors of γ-Secretase and its Modulator

The production of Aβ(1-40) and Aβ(1-42) is the result of the final step of amyloidogenesis, which is carried out by the γ-secretase complex. Inhibiting -secretase was once thought to be a potential method for treating diseases. On the other hand, β-secretase inhibitors have similar problems with substrate promiscuity. Notch protein controls cell multiplication, differentiation, growth and celltransmission, isprimary targets of γ-secretase [31].Similar to β-secretase inhibitors,side effects like off-targetare a big worry[32].

γ-secretase inhibitor like semagacestat (LY450139)decreasesthe levels of Aβin human blood and CSF[33].The worst possible outcomes can be seen in clinical trials (NCT00762411, NCT01035138, and NCT00762411) that recruited more than 3000 patients. According to reports, semagacestat therapy worsened AD patients' capacity to carry out everyday activities (as measured by the ADAS-cog scale).Weight loss, an increased risk of skin cancer, and infections are some of the additional side effects.Avagacestat is one more example ofγ-secretase inhibitor discontinued due to lack of efficacy[34][35][36].

The selective γ-secretase modulator (SGSM), which is linked to significant enzyme inhibition, is theoretically created to prevent undesirable outcomes. Therefore, the goal of these treatments is to prevent the processing of the APP from occurring without the use of other signalling pathways, including Notch [37]. The discovery that several non-steroidal anti-inflammatory medicines (NSAIDs) reduced Aβ peptide (1-42) levels in vivo and in

vitrowas the catalyst for the development of SGSM. Ibuprofen, sulindacand flurbiprofen are a few examples of this category of medication[38].The NSAIDs' well recognized mechanism of action (MOA) is the suppression of the cyclooxygenase (COX) enzyme.R-flurbiprofen (Tarenflurbil), unlike ibuprofen, does not block the COX enzyme, hence its ability to lower levels of Aβ cannot be attributed to this. Sadly, in their respective clinical studies, tarenflurbil and ibuprofen failed to demonstrate efficacy for the treatment of AD [38][39]. CHF5074 is an NSAID without COX inhibitory action, just like R-flurbiprofen. By impeding the γ-secretase complex, CHF5074 prevented the formation of Aβ(1- 42) in vitro [40][41][42].This substance has been labelled as a microglial modulator in recent studies due to the capability of this substance to decrease microglial activation and amyloid burden. The CHF5074 medication improves a number of cognitive assessments and lowers inflammatory marker levels in the CSF, according to the findings of a phase II trial in patients with moderate cognitive impairment (MCI).Interest in NSAIDs as a medicine relatively effective for decreasing Aβ(1- 42) levels was inspired by the prospect that long-term NSAID usage would provide some protection against AD. However, negative outcomes from NSAID-related clinical research demonstrate that this idea has to be improved further[43].

NIC5-15 is another probable instance of SGSM, which is a type of natural cyclic sugar alcohol. It is a chemical that is found in nature and is also referred to as pinitol[40].It is reported that this compound can probably regulate γ-secretase and also reducethe production of Aβwithout affecting the Notch in substrate cutting.Because there is no any reviewed data,therefore, for this chemical, any stated outcomes should be regarded as a statement of future prospects that need hard scientific evidences.However, the compound is asserted to have enhanced memory and cognitive performance in a model of preclinical AD neurological pathology. These findings point to NIC5-15 as a viable therapeutic agent for the treatment of AD as it helps to retain Notch activation, and it has the potential to be an insulin sensitizer, assuming the data are accurate. Since it can prevent microglia from activation, it should also be the subject of research to operate as an anti-inflammatory inhibitor. However, these findings haven't been validated by additional studies yet [26].

3.2. Inhibition of β-Amyloid Peptides Aggregation

Aggregation of Aβ peptides results in the formation of amyloid plaques.To inhibit the production of senile plaques, the following chemicals were produced.

3-amino-1-propaneosulfonic acid (3-APS, Alzhemed, tramiprosate) is the soleagent that inhibits Aβ aggregation that has progressed to phase III studies.This medication was originally created to prevent or reduce the endogenous glycosaminoglycans interaction with soluble Aβ. However, this chemical has been banned in Europe as a result of the phase III clinical trial unsatisfactory results in 2007[44].

A proline-rich polypeptide complex i.e. colostrinin present in human colostrum, ovine, and bovine, lowers Aβ-aggregation and cell neurotoxicity and enhances memory retention in numerous mice models. After 15 months of therapy, participants in a phase II trial who had moderate AD showed modest improvements on the mini mental state examination, but these positive effects were not sustained after an additional 15 months of ongoing therapy [45].

Scyllo-inositol (ELND005) is another example of amyloid anti-aggregation drug that may be taken orally that reduces Aβtoxicity in the hippocampus of mouse. Patients having AD in mild to moderate stages, participated in a phase II clinical trial which lasted for 18-

months using ELND005. The major clinical efficiency objectives of this trial weren't accomplished [46].

Clioquinol and PBT2, the compounds of metal-chelating 8-hydroxiquinolines (8-HQ), were also used in the clinical studies for the treatment of AD [47].Although the precise mode of action is uncertain, it is thought that these kinds of molecules prevent base metals from attaching to the Aβ peptides of brain. It has been suggested that copper ions sticking to Aβ, which results in the metal-mediated formation of reactive oxygen species (ROS), may contribute to the higher oxidative stress levels found in the brains of AD patients[48].Additionally, it was suggested that 8-HQs could balance out the amounts of copper and zinc in cells while preventing Aβ aggregation. Unfortunately, due to lack of efficiency, these compounds failed in clinical development phase II and III[26].

3.3. Aβ Aggregates Removal Compounds

Another possible amyloidogenic pathway-based therapy strategy is promoting the eradication of already existing aggregates as well as plaques. Three distinct tactics have been tested in order to accomplish this.

3.3.1. Transmission Modulation of AβBetween the Peripheral Circulation and the Brain

The transmission of Aβ between the peripheral circulation and the CNS is done by low density lipoprotein receptor-related protein (LRP-1), apolipoproteins(APOE) and receptor for advanced glycation end products (RAGE).The main function of LRP-1 is to increase the Aβ discharge from the brain to blood whereas RAGE enhances Aβ transmission throughout the blood-brain barrier [49][50][51]. Any therapy based on this strategy aims to minimize cerebral amyloid burden by aiming to limit Aβ to the peripheral circulation. A variety of techniques, including the peripheral delivery of LRP-1, have been proposed to achieve this goal.Yet, RAGE inhibitors and modulators are the sole therapeutic candidates which have progressed to the clinical stage. They consist of TTP4000, which successfully completed its phase I trial, and PF-0449470052, which did not give successful results in phase II trials. The findings of this experiment have not been made public[51].

3.3.2. Degradation of Amyloid Plaques by Enzyme Activation

The degradation of aggregates and amyloid plaques is aided by a number of proteases, particularlyplasmin, IDE, neprilysin, angiotensin converting enzyme, endothelin transforming enzyme and metalloproteinases.In AD, there is a reduction in the protein levels associated with these enzymes, which causes Aβ to be produced and deposited.Absolutely no drugs with this MOA progressed to advanced therapeutic uses, despite being a convincing method for creating disease-modifying medications due to a lack of specificity [24][52].

3.3.3. Anti-Amyloid Immunotherapy

Active immunotherapy is the immunotherapy technique intended to improve Aβ elimination in AD to lessen the amyloid burden.In transgenic AD mouse models, the active immunization is effectively tested with Aβ(1-42) or alternative synthetic components.Assays are often predicated on activating microglia's phagocytic capability in order to stimulate immunological responses, T cells and B cells.Human testing was originally encouraging, however, treatment with the very first vaccination (AN1792) resulted in substantial side

effects, forcing the phase II study to be halted. AN1792 was made up of a synthetic Aβ(1-42) peptide and an adjuvant known as QS-21.6% of patients experienced cerebral inflammation brought on by a T cell-mediated autoimmune reaction, whichresult in aseptic meningoencephalitis[26].

To avoid the nonspecific immune response seen with the full-length immunization, shortened Aβ(1-6) peptide sequences were used to create second-generation vaccines. For the first time, Novartis' CAD 106 second-generation vaccine entered the clinical testing phase of research [53].A phase II clinical trial found that 75% of the participants treated had an Aβ-specific antibody response without triggering any unfavorable inflammatory reactions. Janssen developed a drug ACC-001 which have finished two phase II studies (NCT00479557 and NCT01284387), while a third phase II trial (NCT01227564) remain in progress.The pharmaceutical industry nevertheless has given up on further developing this vaccine.There are several other vaccines in various phases of preclinical advancement, particularly tetra-palmitoylated Aβ(1-15) which is remanufactured in a liposome (ACI-24), AF205 and MER5101 [54][55][56][57].

Passive immunotherapy constitutes the delivery of monoclonal or polyclonal antibodies targeting Aβ. Anti-Aβ antibodies are administered intravenously to the patient as part of this treatment. The absence of proinflammatory T cell-mediated immune responses is a benefit of this method over active vaccination. Passive vaccination decreases cerebral amyloid burden and enhances cognition in transgenic rats,despite the fact that the number of amyloid plaques is not greatly decreased. The reason for this might be explained by soluble amyloid oligomers elimination, that are now known to be vital components along the pathophysiologic chain of AD [26].

Monoclonal antibodies which have successfully reached relatively advanced phases in their clinical trials are bapineuzumab and solanezumab[58].Two phase III clinical investigations, though, were unsuccessful in 2012 because they were ineffective for AD patients. Targeting Aβ(1-6) and Aβ(12-28), bapineuzumab and solanezumab are humanizing monoclonal antibodies respectively.Bapineuzumab did not significantly improve cognitive function throughout clinical trials, despite being reported to significantly reduce amyloid deposits in brainand phosphorylated Tau in CSF fluid.AD patients who participated in a research trial were given 400 mg of solanezumab or a placebo once each month for 80 weeks.Statistical significance was not achieved in this study, despite the fact that the results revealed that solanezumab may enhance memory retention in those with moderate AD.The effectiveness of solanezumab in treating AD in patients as well as older people with normal cognitive function who might be in danger of getting AD as they age is now being investigated in phase III clinical trials [59][60].

Researchers are currently studying gantenerumab, another monoclonal antibody, in individuals that put them in danger of developing presenile AD because of the main reason, i.e., sgenetic mutations. In one clinical trial (NCT01760005), the gantenerumab and solanezumab efficacy was assessed in the early stages of the illness.Additionally, two further phase III trials are being conducted to evaluate the effectiveness of gantenerumab in people with mild to moderate AD. A completely human-derived IgG1 antibody called gantenerumab has been created to attach to Aβfibres' structural epitope with great affinity.The recruitment of microglia and subsequent phagocytosis will probably result in amyloid plaque destruction. This idea is supported by experimental research in transgenic mice[26][61].

There have been several monoclonal antibodies created to target Aβ, such as PF-04360365 (ponezumab), MABT5102A and GSK933776A.PF-04360365is a drug that targets amino acids 33–40 at the free carboxy terminal of the Aβ peptide. Meanwhile, MABT5102A has a strong binding affinity for Aβ monomers, fibrils and oligomers. On the other hand, GSK933776A attaches to the N-terminal Aβ(1–5) and shares similarities with bapineuzumab. These medications have diverse methods of action and target various parts of the Aβ peptide, which may have an impact on their efficacy and safety profiles. Additionally, numerous additional passive immunotherapies, including BAN-2401, SAR-228810, and NI-101, are in phase I clinical studies [56][57][61]. Monoclonal antibody crenezumab, often referred to as MABT5102A, has an IgG4 backbone. A recently completed phase II trial, which started in November 2013, is testing crenezumab's effectiveness as well as safety in E280A carriers having no symptoms of the autosomal-dominant PSEN1 mutation [62].

The large-scale clinical research with aducanumab, known as the EMERGE study, demonstrated the efficacy of amyloid targeting in individuals with AD. In the treatment of early-stage AD, the anti-amyloid antibody BAN2401, which targets soluble Aβprotofibrils, has also produced encouraging results. Phase 2 of BAN2401's trial is complete, and phase 3 testing is already taking place. ALZ-801, an oral medication, has also been demonstrated to entirely halt the onset of AD. The effectiveness of ALZ-801 has shown promising results in subgroup analysis of pre-specified groups of patients, specifically those with Aβ oligomers but without plaque binding. Patients with an elevated load of Aβ oligomers who are APOE4 carriers seem to respond better to BAN2401 and ALZ-801 than non-carriers [62]. Table 1 outlines the anti-amyloid drugs currently under investigation.

Table 1: Anti-amyloid drugs undergoing clinical trials[63]:

Drug	**Study Phases**	**Sponsor**	**Duration of Clinical Trial**	**Status (CT.gov ID)**
LY3372993	1	Eli Lilly	Jul 2020 – Feb 2022	Recruiting (NCT04451408)
Abvac40	2	Araclon Biotech	Feb 2018 – Feb 2022	Recruiting (NCT03461276)
ALZ-801	2	Alzheon	Sept 2020 – May 2023	Recruiting(NCT04693520)
APH-1105	2	Aphios	Jun 2021 – Dec 2022	Not yet recruiting(NCT03806478)
Crenezumab	2	Genentech, NIA Banner Alzheimer's	Dec 2013– Feb	Active, not recruiting(NCT01998841)

		Institute	2022	
sDonanemab (LY3002813)	2	Eli Lilly	Dec 2017 – Nov 2021	Active, not recruiting(NCT03367403)
Gantenerumab	2	Roche	Dec 2020 – Feb 2024	Recruiting (NCT04592341)
IVIG (NewGam 10%)	2	Sutter Health	Jan 2011 – Dec 2019	Active, not recruiting(NCT01300728)
Lecanemab(BAN2401)	2	Eisai	Dec 2012 – Feb 2025	Active, not recruiting(NCT01767311)
PQ912	2	Vivoryon Therapeutics AG, ADCS, NIA	Jun 2021 – Jan 2023	Not yet recruiting(NCT03919162)
RO7126209	2	Roche	Mar 2021 – Oct 2024	Recruiting(NCT04639050)
Thiethylperazine (TEP)	2	Immungenetics AG	Nov 2017 – Jul 2021	Active,notrecruiting (NCT03417986)
Aducanumab	3	Biogen	Mar 2020 – Oct 2023	Enrolling by invitation (NCT04241068)
Azeliragon	3	vTvTherapeutics	Jun 2019 – Jul 2023	Active, not recruiting(NCT03980730)
Gantenerumab	3	Roche	Mar 2014 – Apr 2021	Active, not recruiting (NCT02051608)
		Roche	Jun 2018 – Nov 2023	Recruiting(NCT03444870)
		Roche	Aug 2018 – Nov 2023	Active, not recruiting (NCT03443973)

		Roche	May 2020 – Feb 2023	Recruiting, extension study (NCT04339413)
		Roche	Feb 2021 – Dec 2024	Not yet recruiting, extension study (NCT04374253)
Gantanerumab&solanezumab	3	WashingtonUniversity, Eli Lilly, Roche, NIA, Alzheimer'sAssociation	Dec 2012 – Jul 2022	Recruiting(NCT01760005)
Lecanemab (BAN2401)	3	Eisai, Biogen	Mar 2019 – Aug 2024	Recruiting (NCT03887455)
		Eisai, Biogen, ACTC, NIA	Jul 2020 – Oct 2027	Recruiting (NCT04468659)
Solanezumab	3	Eli Lilly, ATRI	Feb 2014 – Jan 2023	Active, not recruiting (NCT02008357)

4. Conclusion

In conclusion, data reveals that AD neuropathology is complex and includes several biological processes. Since the amyloid cascade hypothesis has greatly influencedthe field for more than two decades, a lot of work has been done on preventing and getting rid of Aβ and senile plaques. Nevertheless, despite this amyloid-centric strategy, AD medicines haven't shown that they significantly improve patients' cognitive function. When creating novel experimental treatments, it is important to keep in mind that dendritic spine defects are a contributing component to the cognitive impairment found in this condition. To better comprehend the aetiology of AD, we need take into account activities occurring at the synapse as well as the amyloid cascade theory. It is critical to investigate alternative therapeutic approaches in light of the amyloid immunotherapies and BACE1 program repeated failures. As Aβ oligomers are frequently cited as major factors in AD pathology, inhibitors of these oligomers may prove to be successful AD treatments. Clinical trials may be more successful if they target APOE4 carriers in the early stages of disease and use drug concentrations that decrease Aβoligomers in verified CSF testing.

Abbreviations

Aβ=Amyloid β-protein

Ach = Acetylcholine

AD= Alzheimer's disease

ApoE = Apolipoprotein E

APP = Amyloid precursor protein

BACE1 = β-site amyloid precursor protein cleaving enzyme 1

CNS = Central nervous system

CSF = Cerebrospinal fluid

NSAIDs = Non-steroidal anti-inflammatory drugs

SGSM = Selective γ-secretase modulators

WHO = World Health Organization

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