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Alzheimer's disease: assessing the therapeutic potential of anti-Aβ (Beta-Amyloid) treatments

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Abstract

One of the most common forms of dementia and a neurodegenerative illness is Alzheimer's disease (AD), which is distinguished by impaired memory and cognitive dysfunction. Decades of research have been devoted to determining its etiology, pathogenic processes, and biomarkers to facilitate early identification and clinical investigations for therapy. Neural atrophy and broken connections between neurons are the outcomes of the illness. The amyloid beta (Aβ) cascade is among the most widely recognized and important hypotheses of the numerous hypotheses regarding the pathogenesis of AD. This theory suggests that the breakdown of the amyloid precursor protein (APP) produces Aβ monomers. These monomers are then converted into hazardous oligomers, which in turn form β-sheets, fibrils, and plaques after being formed. The amyloid cascade theory was covered in this review, along with a summary of how it is used to diagnose and treat Alzheimer's. Specifically, we covered the drawbacks, potential, and significant unsolved issues with the anti-Aβ therapy that is now in use, as well as plans for more research and the creation of more workable Aβ-targeted methods to optimize AD early detection and management.

Keywords: Alzheimer’s disease, Amyloid-β oligomers, Beta-Amyloid, Immunotherapy, Monoclonal antibodies.

1. Introduction

One of the main global health concerns is dementia. It was reported by the blueprint of the World Health Organization’s 2022 that around 55.2 million people worldwide are expected to be affected by dementia. However regional variations were also reported in the prevalence rate of dementia among individuals over 60 years old. Europe reported a frequency of 6.5%, Southeast Asia 2.9%, and other areas 3.1% to 5.7%. The most common form of dementia which is responsible for about 60–70% of cases is Alzheimer’s disease (AD) [1]. Since the 1900s, when there was no effective medication to offer an effective cure, AD has been widespread among the elderly population. The AD prevalence was noticed to be increasing in the past 20 years. In 2010, around 36 million instances were reported, and it is expected that by 2030 this number may reach 65.7 million instances [2].

Alzheimer’s disease is mainly characterized by a gradual cognitive deterioration as well as the pathological formation of neurofibrillary tangles and senile plaques in the brain [3]. It is also considered a long-lasting, chronic, progressive disorder with an unidentified cause and undetectable development. This disease consists of three primary types of categorical symptoms: cognitive dysfunction, behavioral disturbances, and difficulties in performing daily activities. Language impairment, memory loss, and executive dysfunction are the characteristics of the cognitive dysfunction category. Behavioral disturbances of the second category, which are known as psychiatric symptoms and non-cognitive symptoms, involve anxiety, depression, delusions, and misapprehension [4]. The last category refers to challenges encountered in accomplishing routine duties, including self-feeding and dressing, driving, orienting oneself, and making judgments. These symptoms range from mild (memory loss) to very severe (dementia) [5].

This has demonstrated the necessity of creating an appropriate treatment plan to slow the disease's growing incidence. The "Amyloid Hypothesis", since its discovery [6], it served as the primary explanation for the etiology of AD in a substantial number of studies aimed at treating the condition for over three decades. According to the amyloid hypothesis, oligomeric amyloid beta (Aβ) peptide buildup and brain deposition are the main causes of Alzheimer's disease [7]. It also was reported that the basic method of action of anti-Aβ medicines is to limit the Aβ generation, prevent its accumulation, and expedite its removal [8]. Therefore, the purpose of this study is to present a sum-

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mary of the therapeutic potential of Alzheimer's disease treatments using anti-Aβ (beta-amyloid) medications.

2. Risk factors of Alzheimer's disease

There are two main risk factors for AD: genetic and environmental. Age is the primary risk factor for the late-onset or senile AD type of illness, which is more correlated with environmental variables [9]. Moreover, many other environmental risk factors for AD are either preventable or modifiable, such as low physical activity, social isolation, low educational attainment, obesity, diabetes, head trauma, systemic arterial hypertension, smoking, hearing loss, social isolation, and depression [10].

On the other hand, when it comes to the genetic risk factor, the autosomal dominant forms of AD are primarily caused by mutations mainly in the genes encoding the amyloid precursor protein (APP), presenilin 1, or presenilin 2, which are found in 70% of cases. Autosomal dominant forms are characterized by being relatively rare, having an early onset, manifesting before the age of 65, and having an autosomal inheritance pattern [11].

3. Pathogenesis of Alzheimer's disease

During AD, both the mass and number of neurons diminish gradually as a result of severe brain atrophy [2]. Many hypotheses for the AD pathogenesis and progression have been proposed by the scientists. Neurotransmitter imbalance, disturbance of the blood-brain barrier, and neuroinflammation are some of the neuropathological alterations that have been suggested as potential etiology theories. However, the two main pathological characteristics hypothesized are the development of neurofibrillary tangles and amyloid-β (Aβ) plaques [12]. The amyloid β protein (Aβ) has gained attention for its role in AD since the discovery of Glenner and Wong [13] that the Aβ is the main constituent of extracellular amyloid plaques in AD. From that point on, the "amyloid cascade hypothesis"[6] has emerged as a major explanation regarding the pathogenesis of AD, with Aβ being seen as a driver of the disease's degenerative processes [3].

Moreover, the development of senile plaques (SP) as a consequence of the deposition of Aβ is one of the primary pathogenic characteristics of AD [14]. The synthesis and aggregation of amyloid beta (Aβ) peptides in the extracellular matrix of brain cells is the central mechanism behind a series of pathogenic and non-pathogenic processes that are included in the amyloid hypothesis (Fig. 1) [2].

The non-pathogenic pathway of Aβ production started when the enzymes α-, β-, and γ-secretase broke the precursor protein of amyloid (APP). This process resulted in the production of the APP intracellular domain (AICD) and extracellular soluble fragments. These fragments are characterized by being safe, improving synaptic plasticity, controlling neuronal excitability, and providing protection against oxidative and metabolic stress [14].

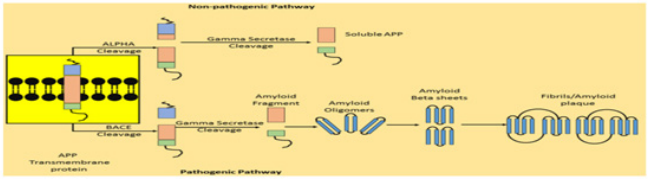

Fig. 1. The theory of the amyloid cascade. BACE-Beta-site APP-cleaving enzyme; APP-Amyloid precursor protein [2].

While in the pathogenic pathway, beta-site APP-cleaving enzymes (BACEs), which are also known as β-secretases, play a fundamental role in promoting APP cleavage [15]. Furthermore, extracellular Aβ42 fragment monomers are produced when β- and γ-secretase cleaves APP. These Aβ42 fragment monomers will then develop in loose clusters of Aβ42 fragments known as soluble oligomers [16]. After that, sheet-like structures known as beta-sheets (β-sheets) will result from the arrangement of oligomeric structures that will further together create organized fibrils known as β-plaques. Deformed cell membranes and changed cell architecture are the outcomes of plaque deposition on the surface of neurons [17].

However, when it comes to toxicity, the plaques are less toxic than oligomeric entities. Inter-neuronal signal transmission is lost when neuronal communication is impaired by the synaptic buildup of Aβ plaques [18]. Disruption of brain cells and ultimately leading to cell death will result from the recurrent deposition and buildup of Aβ plaques, which is induced by neuronal immune response [2]. It should be mentioned that the development of Aβ plaque indicates AD [19].

4. Treatment of Alzheimer's disease

When it comes to AD treatment, the acetylcholinesterase inhibitors (AChE) (which are also known as cholinesterase inhibitors (ChEIs)) and N-methyl-d-aspartate (NMDA) receptor blockers are the two categories of drugs that have been approved by the Food and Drug Administration (FDA) for managing this disease. The first category (ChEIs) mainly function through preventing acetylcholine degradation in the early stages of AD. The NMDA receptor blocker, on the other hand, stimulates the disease progression with the help of AChE inhibitors during the moderate-to-severe stage of AD [20].

Tacrine, Donepezil, Carbalatine, Galanthamine, and Memantine are the five drugs that were approved by the FDA in addition to the Lecanemab drug, which was approved recently. The following drugs (Tacrine, Donepezil, Carbalatine, and Galanthamine) are examples of AChEIs. Their main mode of action is inhibiting the acetylcholine destruction in the synaptic gap, which will preserve neuronal activity, increase cholinergic effects, and enhance memory and learning [21]. Memantine is an example of an NMDA receptor antagonist by which the neuronal apoptosis as well as the neurotoxicity of excitatory amino acids are reduced [22]. However, it should be noted that these medications do not treat AD because they only control its symptoms and postpone its development. When it comes to lecanemab (BAN2401), which is an IgG1 monoclonal antibody, it was reported that it has the ability to decrease amyloid markers in individuals with early AD [23]. Despite that, further investigations are needed to ascertain the efficacy and safety of this medication [24].

However, two main drawbacks negatively impact the use of many new drugs under test for AD treatment. These drawbacks are the severe side reactions of those drugs or inadequate effectiveness. The pathogenic characteristics of AD that have been the focus of current clinical studies include tau protein, amyloid plaques (Aβ), mitochondria targeting, as well as multi-targets. The FDA authorized the use of aducanumab, which is an anti-Aβ monoclonal antibody (mAb), for AD treatment. This approval sparked

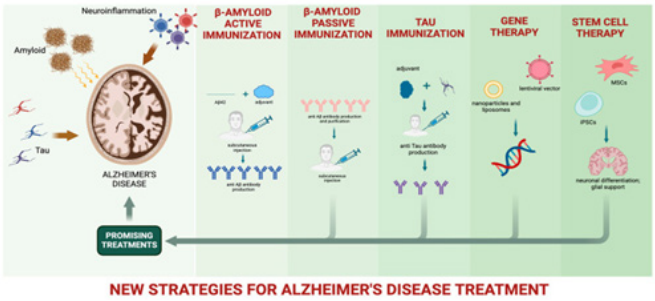

Fig. 2. AD pharmacological treatment Strategies [25].

intense discussion and much enthusiasm among doctors [25]. Recently, pharmacological treatments for AD treatment have been developed positively (Fig. 2). But finding the ideal AD treatment still needs a lot of time [26]. Therefore, the proposed therapeutic approaches for AD were categorized into four primary categories: therapy targeting drugs [21].

In order to stop the accumulation of Aβ, a lot of research that focuses on addressing therapeutic approaches to the pathophysiology of AD as well as the hypothesis of the Aβ cascade hypothesis (ACH) was introduced over the last thirty years [27]. Currently, AD research is mostly focused on testing disease-modifying treatments, with the Aβ target making up around 15.4% of these trials [28]. Passive immunization, active immunization, and secretase inhibitors are known to be the key approaches of AD therapies that target Aβ [29].

Passive immunotherapy is one of the Aβ clearance strategies in which the key passive immunotherapy for AD is monoclonal antibodies (mAbs) [30]. There are several mechanisms used to enhance the Aβ clearance using humanized mAbs, such as enhancing complement activation and macrophage phagocytosis by antigen opsonization, prevention of oligomer or fibril formation, antibody-mediated alteration of the Aβ monomer's structure, as well as promoting Aβ clearance from the central nervous system through antibody-mediated peripheral reduction of Aβ [29]. Recently, mAb-based clinical studies have been promoted to activate Aβ clearance from the brain. Additionally, it has been demonstrated that mAbs are ineffective against monomers but effective against Aβ plaques targeting various Aβ epitopes [31].

There are several anti-Aβ mAbs like bapineuzumab, lecanemab, aducanumab, and solanezumab that have been tested as immune therapy methods for the treatment of AD (Table 1). Aducanumab was the first anti-Aβ monoclonal antibody that was approved by the FDA in 2021 for AD treatment, as was lecanemab, which was recently approved [32]. During the experiment, lecanemab (BAN2401), an IgG1 monoclonal antibody, was tolerated favorably; however, amyloid-related imaging abnormalities (ARIA-E) were seen by a few patients [23].

The identification of amyloid-related imaging abnormalities (ARIA) was a result of increased MAB usage. ARIA has been further divided into two groups: ARIA-H, which denotes bleeding, and ARIA-E, which denotes edema and/or effusion [33]. Moreover, increased vascular permeability after an inflammatory reaction is assumed to be the etiology of ARIA, resulting in the extravasation of proteinaceous fluid and blood products. Though they are mostly asymptomatic and can only be diagnosed by MRI, patients with ARIA may exhibit headaches [34]. It should be noted that vascular extravasation events can cause ARIA-E (proteinaceous fluid leakage products) and ARIA-H (blood products leaking through damaged vessel walls) in vessels with already available amyloid vascular disorders after anti-Aβ therapy is initiated [35]. The degree of vascular permeability increase is contingent upon the local inflammatory reaction, the effectiveness of amyloid clearance, and the severity of previous amyloid angiopathy [36].

Furthermore, it was reported that using the Lecanemab multicenter, double-blind, 18-month Phase III trial has the ability to reduce amyloid markers in the early stages of AD, but in order to make sure of its safety and efficacy, longer trials are needed [24]. These mAbs identify epitopes according to the particular region and conformations of Aβ and exhibit different preferences for polymorphic variations. The effects of the mAbs on the p181-tau level varied, but all of them can lower the levels of Aβ peptides in plasma or cerebrospinal fluid (CSF) to varying degrees at different dosages [37].

Although the anti-amyloid mAbs have different characteristics that help distinguish them, they also have some similar characteristics. From the perspective of their mechanisms of action, all of them are linked to ARIA, generate a notable decrease of Aβ on amyloid positron emission tomography (PET), and target high molecular weight fibrillar Aβ aggregates [38]. Pharmacokinetic (PK) characteristics, including infusion rate and titration schedule, vary between the mAbs, as do the kind and range of amyloid species targeted [39]. Even though the precise definition of early AD in relation to acceptable severity varies between the mAb trials, these differences may influence patient selection for treatment with a particular agent. They are common in that they encompass early AD (mild cognitive impairment [MCI] associated with AD as well as mild AD dementia) as the participant population [40].

An additional approach for Aβ clearing is active immunization, in which the natural immune response and production of Aβ antibodies are induced by the addition of Aβ fragments. This method proved its effectiveness in mouse models [41]. However, there are a few issues that need to be managed when producing anti-Aβ vaccines, such as the self-tolerance that should be destroyed. In addition to that, since normal cells also contain Aβ, autoimmune response stimulation may be associated with unfavorable consequences, including meningoencephalitis linked to a T-cell-mediated reaction against Aβ [25].

Furthermore, it was found that individual factors like age and immune status, as well as vaccine-related factors like the chosen epitope (antibodies targeting a particular epitope may work better than others, ideally favoring the removal of brain Aβ plaques), can all affect how the body reacts to vaccination [42]. Moreover, it was reported that modification, management, or termination of active immunological responses is a challenging process, particularly in elderly individuals [41].

Aβ is produced by sequential cleavage of Aβ precursor protein (APP) by β-secretase and γ-secretase which is considered the last method for AD therapies. BACE1 (β-site APP cleaving enzyme-1) is a unique β-secretase; its absence can prevent the production of Aβ, making BACE1 an important therapeutic target. Hence, strategies focused on BACE1 inhibitors, γ-secretase inhibitors (GSI), and

Table 1. Anti-Aβ monoclonal antibody treatments for AD patients and animal models [37].

Pre-clinical and clinical studies	Anti-Aβ monoclonal antibodies	Immune response and pathological changes after therapies	Clinical profiles change after therapies	Side effects
Tg2576 transgenic mice Prodromal or mild AD patients	Aducanumab	Binding parenchymal Aβ, and soluble and insoluble Aβ↓(mice) Amyloid plaque at week 54 ↓by PET scan (patients)	Slowing clinical progression via detections by MMSE and CDR-SB; No changes on NTB or FCSRT (patients)	ARIA-E and superficial siderosis (patients) ARIA-E 35.2%, ARIA-E was highest in ApoE4 + subjects
Mild to moderate AD	Bapineuzumab	No significant changes in whole-brain volume.	No significant improvement in clinical symptoms (ADAS-Cog/11, DAD, NTB, Z-score, CDR-SOB and Dependence Scale)	ARIA-E and cerebral microhemorrhage ↑
Prodromal AD patients	Gantenerumab (105 or 225 mg/4 weeks)	Biomarkers of neural and synaptic degeneration↓; PET SUVr↓ in 225 mg dose group; MRI volumetry: No difference; CSF: t-tau and p-tau↓	No significant improvement in clinical symptoms in 105 or 225 mg (CDR-SB, ADAS-Cog 13, MMSE, and FAQ, FCSRT with immediate recall total recall, CANTAB, and NPI-Q)	ARIA-E 6.6% (105 mg), 3.5% (225 mg). ARIA-H 22.9% (105 mg), 16.2% (225 mg)
Prodromal to moderate AD	Gantenerumab (1200 mg/4 weeks)	PET: resulted in robust Aβ plaque removal at 2 years	Slowed clinical decline with higher Aβ removal in 1,200 mg group (CDR-SB, ADAS-Cog 11, and MMSE)	
DIAD mutation dominantly inherited Alzheimer's disease	Gantenerumab (1200 mg/4 weeks)	PiB-PET: brain Aβ deposition ↓; CSF: Aβ42↑, t-tau and p-tau 181 ↓, NfL↑ slowed at year 4. 18F-FDG-PET and volumetric MRI: no difference in brain cortical metabolism or atrophy	No difference in cognitive decline between the gantenerumab and control	ARIA-E 19.2%
Early Alzheimer's disease	Lecanemab (10 mg/kg biweekly)	CSF: Aβ42↑, p-tau ↓ PET SUVr: brain Aβ↓at 18 months	Improvement in clinical symptoms (ADCOMS, ADAS-Cog14, CDR-SB) Greater reductions of cognitive decline in ApoE4 + subjects	ARIA-E 10% ARIA-H: 10.7% ARIA-E and ARIA-H was higher in ApoE4 + subjects Infusion reactions 19.9%
Mild AD	Solanezumab	Total Aβ40 and Aβ42 in CSF↑ Unbound Aβ40 in CSF↓ Unbound Aβ42 in CSF↑	No significant improvement (ADAS-cog14, MMSE, ADCS-iADL, FAQ, CDR-SB score)	Mild AD
DIAD mutation dominantly inherited Alzheimer's disease		CSF NfL ↑, Aβ PET, t-tau or p-tau181: No difference Brain cortical metabolism 18F-FDG-PET or atrophy: No difference	Faster cognitive decline in the solanezumab group vs. the control groups	ARIA-E was lower in solanezumab group

γ-secretase modulators (GSM) have also been developed for the treatment of AD [42].

It has been difficult to produce AD medications, as evidenced by the majority of clinical trials using these mAbs yielding mostly unfavorable findings [37]. The two primary issues associated with these mAbs' treatments are their inability to produce clinically meaningful effects in patients with prodromal or clinically apparent dementia, as well as the elevated rate of ARIA that some mAbs trigger, which suggests that the risk of side effects surpasses the advantages of the treatments [43]. Due to the inability to meet primary objectives, the majority of clinical trials, which include these anti-Aβ mAbs therapies, were stopped.

On the other hand, tau immunization is a complicated procedure that targets tau protein. Since tau is involved in many vital physiological processes, unconditioned inhibition of its synthesis may have serious adverse repercussions. It is also difficult to determine which tau isoform to target in order to prevent neurodegenerative effects because tau comes in several forms. Although they have not proven any clinical benefits, selective inhibitors of tau-phosphorylation were previously tested and demonstrated to decrease tau aggregation and Aβ accumulation [36].

Another treatment option is gene therapy, a novel and promising therapy that concentrates mostly on a genetic target but can also alter the molecular and genetic environment. It focuses on beta-amyloid plaques, decreases inflammation and brain cell loss, and replaces damaged neurons. However, there are few studies that can support this method, and its significance in AD is controversial and subject to argument [44].

Moreover, for individuals with AD, stem cell (SC) therapy can provide long-lasting advantages because of

its potential immunomodulatory, anti-inflammatory, and regenerative characteristics. Currently, only mesenchymal stem cells (MSCs) are studied in AD patients, despite the fact that there are four main SC types that may be useful for treating AD: embryonic, mesenchymal, neural, and induced pluripotent SCs. Due to their high accessibility, diverse methods of administration, minimal immune response, and a broad range of differentiation potential (even if they cannot develop into neurons), MSCs are the most controllable cells [45].

5. Future directions for Aβ antibodies

Furthermore, because of the restricted blood-brain barrier (BBB) permeability (which is generally around 0.1% of the injected dosage), peripheral delivery fails to be suitable for transferring antibodies to the brain at an adequate level [46]. As a result, efforts to create antibodies with high BBB permeability have gained interest over the years. It is anticipated that these modified antibodies would decrease doses and increase clinical effectiveness, and this may help to mitigate adverse effects, including ARIA [47]. Denali's Antibody Transport Vehicle (ATV) technology serves as one illustration of achieving significant BBB penetration. Iron entry into the brain to preserve iron homeostasis is facilitated by the transferrin receptor. Accordingly, endothelial cell receptors may be bound by an antibody containing a transferrin receptor 1-binding domain, allowing for active receptor-mediated transport via the BBB (Fig. 3) [46].

In order to maximize brain exposure and decrease ARIAs, Biogen revealed that it will be using ATV technology to generate next-generation Aβ antibodies [48]. Along with that, Eisai declared that they are looking at using their original brain transport system to create a more advanced form of lecanamab [49]. The Brainshuttle technology, which enables a Fab antibody fragment to bind transferrin receptor 1, was additionally developed by Roche. Their new antibody, gantenerumab, in combination with trontinemab and Brainshuttle really improved BBB crossing and reduced the number of ARIAs needed to clear Aβ plaques. It is made possible for tiny molecules to travel through the BBB by the brain shuttle. When released, this tiny biomimetic molecule can transport therapeutic compounds across the blood-brain barrier for maximum efficacy. The delivery of mAbs with fully functioning bivalent immunoglobulin G (IgG) antigen binding is made possible by Brain Shuttle (BS) technology. This is achieved by linking the C-terminal region of the heavy chain's constant region (Fc) with the BS module. Additionally, this Brain Shuttle-modified anti-Ab demonstrated markedly improved brain penetration and amyloid plaque reduction by attaching the BS module to an anti-beta-amyloid (Aβ) mAb [50].

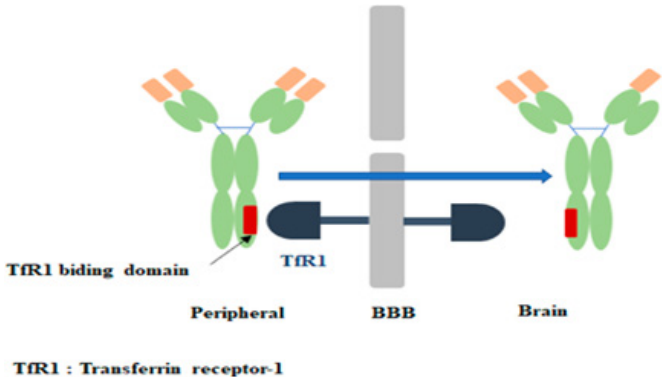

Fig. 3. An outline of the Denali Antibody Transport Vehicle. This technology achieves high BBB penetration by binding to transferrin receptors on endothelial cells, allowing active receptor-mediated iron homeostasis [46].

Through the use of such technologies, in-depth studies on brain-penetrating Aβ antibodies may be able to shed light on the process underlying ARIAs and lead to a large dose decrease, offering AD patients more inexpensive treatment alternatives. The references emphasize the effectiveness of combining anti-Ab and anti-Tau therapies. However, the use of long-acting anti-Ab treatments has not been explored, and there are safety concerns due to a high risk of ARIA. Also, a long-acting injectable dosage may be utilized to improve patient and caregiver convenience if a brain-penetrating Aβ antibody at a low dosage is found to be safe [46].

6. Conclusion

The neurodegenerative condition known as AD has a complicated etiology that involves several targets and pathways. Year by year, the burden of AD rises due to the population's ongoing aging. Unfortunately, it has been a while since a new medication was licensed for AD treatment. Therefore, since AD is thought to be caused by Aβ, and because Aβ is thought to be the primary pathogenic alteration in AD, anti-Aβ medication is potentially beneficial. Moreover, a growing body of clinical research indicates the potential for an important development soon with the application of anti-amyloid monoclonal antibodies as a successful treatment for AD, but this needs further investigation to make sure of the treatment effectiveness and safety.

Abbreviation

Aβ cascade hypothesis: ACH; Acetylcholinesterase inhibitors: AChE; Alzheimer's disease: AD; APP intracellular domain: AICD; Amyloid precursor protein: APP; Amyloid-related imaging abnormalities: ARIA-E; Antibody Transport Vehicle: ATV; Amyloid beta: Aβ; β-site APP cleaving enzyme-1: BACE1; Beta-site APP-cleaving enzymes: BACEs; Blood-brain barrier: BBB; Cholinesterase inhibitors: ChEIs; Cerebrospinal fluid: CSF; Food and Drug Administration: FDA; γ-secretase inhibitors: GSI; γ-secretase modulators: GSM; Monoclonal antibodies: mAbs; Mild cognitive impairment: MCI; N-methyl-d-aspartate: NMDA; Positron emission tomography: PET; Pharmacokinetic: PK; Senile plaques: SP; Beta-sheets: β-sheets.

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