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Chapter

Future Treatment of Alzheimer Disease

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Abstract

Alzheimer's disease is an age-related progressive neurodegenerative disorder. The two major neuropathologic hallmarks of Alzheimer's disease (AD) are extracellular Amyloid beta (Aβ) plaques and intracellular neurofibrillary tangles (NFTs). A number of additional pathogenic mechanisms, possibly overlapping with Aβ plaques and NFTs formation, have been described, including inflammation, oxidative damage, iron dysregulation, cholesterol metabolism. To date, only symptomatic treatments exist for this disease, all trying to counterbalance the neurotransmitter disturbance. To block the progression of the disease they have to interfere with the pathogenic steps responsible for the clinical symptoms, including the deposition of extracellular amyloid β plaques and intracellular neurofibrillary tangle formation, inflammation and stem cell. In this review, we discuss new potential disease-modifying therapies for AD that are currently being studied in phase I–III trials.

Keywords: Alzheimer, secretase modulators, anti-amyloid agents, stem cell

1. Introduction

Alzheimer's disease (AD) is an age-related progressive neurodegenerative disorder characterized by progressive memory loss, cognitive impairment and functional decline. AD is described as a multifactorial disease and several mechanisms significant roles in disease pathogenesis. Through an improved understanding of the molecular mechanisms underlying pathogenesis of AD, it is possible to develop novel, effective therapeutic methods in order to prevent onset and progression of AD. A better understanding of the molecular mechanisms underlying pathogenesis of AD makes available to a basis for development of novel, effective therapeutic strategies to prevent onset and progression of AD.

The formation of intracellular neurofibrillary tangles that are composed of hyperphosphorylated tau proteins [1] and accumulation of extracellular amyloid plaques are the fundamental neuropathological changes noticed in AD brain. Aβ and tau are two key/important proteins, have a main function in the pathogenesis of AD. Amyloid cascade hypothesis and tau hypothesis have been based on the causative factors in AD pathogenesis. While one of these hypothesis proposes that AD starts with the accumulation of Aβ, the other one suggests that AD starts with the accumulation of p-tau.

Amyloid cascade hypothesis: in 1992 Hardy and Higgins constructed the amyloid-cascade hypothesis [2]. According to this hypothesis, formation of pathological Aβ plaques, neurofibrillary tangles, synaptic loss, neurodegeneration and ultimately dementia in AD are caused by a cascade harming synapses and neurons has been triggered by Aβ and its aggregates. Aβ peptides are natural products of brain metabolism. AD is associated with the disruption of the balance between production and clearance of Aβ. Aβ accumulation in the brain induces oxidative stress and inflammatory response thus leads to neurotoxicity which contributes to impairment of cognitive functions. Several pathological events like excitotoxicity, synaptic and mitochondrial dysfunction, loss of calcium homeostasis, endoplasmic reticulum stress, oxidative stress and inflammation may occur as a result of Aβ aggregates. In spite of the role of Aβ in AD, only amyloid-cascade hypothesis is not sufficient to explain AD pathogenesis, because removal of Aβ did not halt AD pathology [3].

Tau hypothesis: tau is an intracellular protein which is a member of microtubule-associated proteins family. This protein family promotes microtubule assembly and stabilization. Tau has neurotoxic effects when hyperphosphorylated due to loss of its normal function. Hyperphosphorylated tau promotes the formation of paired helical filaments which would eventually evolve into NFTs, dystrophic neurites, and neuropil threads [4]. Abnormal hyperphosphorylation of tau is a component of neurofibrillary tangles that is a key player of neurodegeneration and has been isolated from AD brain in the 1990s [5].

Although both hypotheses suggest primal roles of Aβ and tau protein in AD pathogenesis, increasing evidence suggests that there may be a crosstalk between two pathologies. However, the mechanisms linking Aβ toxicity and tau hyperphosphorylation have not been exactly clarified yet.

2. Pathogenic mechanisms in Alzheimer's disease

2.1 Oxidative stress

Oxygen metabolism generates free radicals such as reactive nitrogen species (RNS) and reactive oxygen species (ROS) including superoxide anion and hydroxyl radical. One of the early changes observed in AD patients is increased oxidative damage. It has been shown that the percentages of 8-hydroxydeoxyguanosine (8OHdG) and 8-hydroxyguanosine (DNA and RNA oxidation markers), 4-hydroxynonenal, and F2-isoprostanes (lipid peroxidation markers), protein carbonyls and 3-nitrotyrosine (protein oxidation markers), and malondialdehyde (MDA), have been increased in AD brains [6]. Although the data is highly limited, oxidative stress may also influence hyperphosphorylation and polymerization of tau protein. Although oxidative stress has an important role in AD, it is still disputed whether it plays a causative role in the disease or secondary to the pathological changes observed in AD [7].

2.2 Neuroinflammation

Neuroinflammation is described as a process involving activation of natural immunity in the brain. The functions of neuroinflammation can be explained as protecting central nervous system from infectious insults, injury or diseases. Microglia are has a significant role in neuroinflammation. Transgenic animal models of AD have demonstrated that neuroinflammation is enhanced around amyloid plaques [8]. According to Bellucci et al. inflammation is the key player in the tauopathies for neurodegeneration [9]. It has been shown that production of enzymes

(COX-2) and proinflammatory cytokines (IL-1β) are boosted in tau-positive nerve cells in spinal cord and brainstem. Pursuant to these results of the research, neuroinflammation might be triggered through NFTs by activating microglia. It is found that suppression of neuroinflammation is related to improvements in behavioral and cognitive deficits in AD mouse models and is in harmony with decline in hyperphosphorylated tau and Aβ plaques in brain. It is efficient to treat with interleukin-1β (IL-1β) antibodies or anti-tumor necrosis factor-α (anti-TNF-α) in order to reduce the pathology in animal models of AD. It is noted that Aβ secretion and the expression and activity of β-secretase have been reduced by peroxisome proliferator-activated receptor-γ [PPAR-γ] agonists and nonsteroidal anti-inflammatory drugs [NSAIDs] [10]. It is suggested that suppression of neuroinflammation with NSAIDs rescues memory and cognitive decline. While retrospective epidemiological studies have proven that prolonged treatment with NSAIDs delays onset of AD when initiated early stage or before disease initiation, its effectiveness has not been demonstrated in neither mild nor moderate forms of AD [11].

2.3 Metal toxicity

Iron, zinc and copper are important elements for neuronal function. During the aging, these metal ions accumulate in the brain, consequently contribute to neurodegeneration. Zinc, copper and iron have been found to be accumulated within the core and periphery of senile plaques and these metals have been suggested to be involved in Aβ aggregation and oxidative damage. Metal chelation is a therapy based on binding and removing to metal ions. This therapy can provide an advantageous against oxidative stress in AD. Desferrioxamine and clioquinol are several examples of treatment methods with metal chelators. And these methods have caught some success in order to alter the progression of AD [12]. Therapeutic approaches focusing on the improvement of metal balance are one of the popular subjects of current researches in the field of AD.

2.4 Mitochondrial dysfunction

Mitochondrial dysfunction has a significant function in brain aging and AD. Swerdlow and Kan suggested mitochondrial cascade hypothesis for sporadic form of AD in 2004 [13]. This hypothesis proposes that mitochondrial dysfunction exists early in disease pathogenesis and causes, NFT formation, Aβ deposition and synaptic loss, the mitochondria is vulnerable to oxidative stress because of lack of DNA repair activity and is the significant source of ROS in the central nervous system. Oxidation of mitochondrial DNA presents it vulnerable to somatic mutations which augments mitochondrial dysfunction. Mitochondrial dysfunction has been proposed to trigger onset of neuronal degeneration in AD. It is showed that Aβ accumulates in mitochondria from AD patients. Tau protein might also be included in mitochondrial dysfunction in synapse, indirectly.

2.5 Brain insulin resistance and insulin deficiency

Type 2 diabetes mellitus is a risk factor for AD and these two disorders share many common pathological pathways. Impaired glucose metabolism is related to rising oxidative stress and accumulated advanced glycation end products. Insulin is even produced in brain tissue itself. Insulin receptors are mostly located in the cerebral cortex, cerebellum, hypothalamus, hippocampus and olfactory bulb that are the cognition pertinent areas of the brain. Brain glucose utilization and insulin signaling are impaired in AD. AD is related to a reduction in the levels of insulin in

the cerebrospinal fluid (CSF), in the ratio of CSF insulin/plasma insulin, a decline in the expression of insulin receptors and a rise in fasting plasma insulin levels. Impaired insulin signaling might influence AD pathogenesis via tau hyperphosphorylation, acetylcholine signaling and Aβ metabolism. Insulin stimulates the expression of choline acetyltransferase, the enzyme responsible for acetylcholine synthesis. Therefore, decreased insulin levels, as well as insulin resistance, can ultimately contribute to a decrease in acetylcholine in AD brains [14].

2.6 Future therapeutic approaches and management of AD

Alzheimer's disease [AD] is one of the most challenging threats to the healthcare system. The current therapeutic goals are to reduce amyloid levels, prevention of amyloid aggregation/toxicity and tau phosphorylation/aggregation. There is also a major improvement in understanding the role of cholinesterase [ChE] in the brain and the function of ChE inhibitors in AD Academic research has carried out on the system of a new generation of acetyl- and butyryl ChE inhibitors and test for AD in clinical experiments on human beings. Next to this alternative strategies for treating or slowing the progression of AD, like vaccination, anti-inflammatory agents, cholesterol-lowering agents, antioxidants and hormone therapy, are also studied. Although several anti-amyloid β compounds have been examined in clinical trials as potentially useful drugs, all of them have failed to show significant benefits so far. Tau-targeted drugs have been developed and have entered clinical trials recently. The improvements on early diagnostic biochemical markers will be useful to increase for better monitoring the course of the disease and to evaluate different therapeutic strategies [15].

Academic research of Alzheimer's disease consists three steps. The first one is to select a high-risk population with current evidence and to provide this population primary prevention. The goal of this first stage is to be able to manage modifiable risk factors. Second is to diagnose patients at the preclinical phase, which starts 10–20 years before symptoms occur. Researchers aim to find new and improve existing neuroimaging techniques, CSF investigations and laboratory and genetic studies. The third step is to discover disease-modifying molecules. Researchers are aiming to inhibit extracellular amyloid plaque accumulation and to inhibit intracellular tau-based neurofibrillary tangles accumulation [16].

2.6.1 Anti-amyloid agents

One of the main suggested pathophysiological processes is 'amyloid cascade hypothesis'. All autosomal dominant AD genetic forms are the result of mutations of amyloid metabolism encoding genes. Also clinical and experimental data indicates toxic effects of accumulated amyloid plaques. Amyloid directed therapies can be classified in three different classes: amyloid anti-aggregates, secretase modulators and immunotherapies [17].

2.6.2 Secretase modulators

To reduce Aβ production, researchers focused on modulate enzymes that breakdown amyloid precursor protein [by stimulating α secretase or inhibiting γ and β secretase activity]. While effective α secretase was infrequently, various γ and β secretase inhibitors improved. γ secretase plays a decisive role in Aβ generation but this enzyme has several cleavage actions including notch receptor signaling so that γ secretase inhibitors have significant side effects. β secretase inhibitors also failed to show disease-modifying effects but there are still ongoing studies [17].

2.6.3 Amyloid anti-aggregates

Another strategy is to prevent aggregation of amyloid in non-soluble forms. Although new studies report soluble form of Aβ also have toxic effects. It's known that Aβ forms oligomers, fibrils and then deposition of amyloid plaques exist. Tramiprosate, colostrinin, clioquinol are some of the studied anti-Aβ aggregation agents. There were no effects or minimal effects phase II and III anti-Aβ aggregation agents trials on cognition. There are ongoing projects to improve new molecules [18].

2.6.4 Amyloid removal [immunotherapy]

Although it is not proven (exactly) how immunotherapy might attenuate Aβ plaques in the brain, some mechanisms have postulated. Therapeutic goal is to induce a humoral immune response to fibrillary-Aβ42 or passive administration of anti-Aβ antibodies. First studies of active vaccination were halted because of the induction of serious side effects. There are ongoing phase I–III studies with active and passive immunization (CAD106, bapineuzumab, solanezumab, intravenous immunoglobulin) [18].

2.6.5 Tau-based therapies

Tau is a microtubule-associated protein and the MAPT gene encodes tau. Assembling microtubules and regulating axonal transport are various functions of tau. It is proven that hyperphosphorylated tau causes disruption of mitochondrial respiration and axonal transport. It should be emphasized that tau hyperphosphorylation is also considered as a pathologic sign of other neurodegenerative diseases, including, frontotemporal dementia with parkinsonism (FTD-P), corticobasal degeneration, progressive supranuclear palsy and Pick disease. Mutations of tau encoded MAPT1 gene causes FTD-P. Therefore neurodegeneration without amyloid deposition can be driven by tau dysfunction. Tau-based therapies are still at conceptual stages and include passive immunization against tau, preventing tau hyperphosphorylation and anti-aggregates of tau. Methylthioninium chloride and lithium are some of the elements with current studies. There are also some experiments ongoing about anti-tau vaccines at AD [19].

3. Treatments that failed in clinical trials

Only four cholinesterase inhibitors (tacrine, donepezil, rivastigmine, galantamine) and an *N*-methyl-D-aspartate (NMDA) receptor AD antagonist (memantine) are approved for the treatment of AD. These five drugs are all symptomatic treatments. No new drugs have been approved for treatment of AD since 2003. Disease modifying drugs (DMD) is the real goal in AD treatment. However, success rate is extremely low for Alzheimer treatment research. Until today, anti-inflammatory (NSAİD, steroids), antioxidant (selenium, vitamin E), anti-ischemic (statin, aspirin), cholinergic (lecithin), nutrients (Omega-3, vitamins B, folic acid), monoclonal antibody (bapineuzumab, solanezumab) treatments have failed (**Table 1**). The overall failure rate was 99.6% (0.4% success) in the decade spanning from 2002 to 2012 [20]. Many explanations have been proposed for the failures of trials of DMD for AD, including starting therapies at the late phase of disease, wrong or nonspecific treatment targets, incorrect doses, the lack of homogeneity of individuals (genetic, ethical, temporal and medical grounds), nonspecific or blunt trial design [21, 22]. On the other hand, pathological changes may not correlated with cognitive deficits

Agent	Proposed mode of action	Reason	Reference
Ganstigmine	Acetylcholinesterase inhibitor	Side effects (headache, nausea, vomiting, anorexia)	Racchi et al. [23]
Metrifonate	Cholinesterase inhibition (irreversible)	Side effects (neuromuscular dysfunction, respiratory failure)	Arrieta et al. [24]
Lecithin	Major dietary source of choline	There is no significant benefit of lecithin for Alzheimer's disease or Parkinsonian dementia	Higgins and Flicker [25]
Ibuprofen	Anti-inflammatory, NSAİD	No evidence yet exists ibuprofen is efficacious in Alzheimer's disease	Tabet and Feldman [26]
Rofecoxib	Cyclo-oxygenase-2 inhibition	No significant differences between treatments were found for the ADAS-cog score	Reines et al. [27]
Aspirin, steroid	Anti-inflammatory	No significant improvement in cognitive decline for aspirin and steroid	Jaturapatporn et al. [28]
Latrepirdine	Antihistamine drug	There is no effect of latrepirdine on cognition and function in mild-to-moderate AD patients	Chau et al. [29]
Selegiline	Monamine oxidase inhibition	The evidence of benefit using standardised global cognitive scales was extremely limited. There is not yet enough evidence to recommend its use in practice	Birks and Flicker [30]
Pravastatin	Lowers plasma cholesterol and lipoprotein	Pravastatin had no significant effect on cognitive function or disability	Shepherd [31]
Simvastatin, pravastatin	Lowers plasma cholesterol and lipoprotein	There is no evidence that statins prevent cognitive decline or dementia	McGuinness et al. [32]
Omega-3 polyunsaturated fatty acids	Essential dietary nutrient	There is not convincing evidence for the efficacy of omega-3 PUFA supplements in the treatment of mild to moderate AD	Burckhardt et al. [33]
Vitamin E, selenium	Antioxidant supplement	Antioxidant supplements did not prevent dementia	Kryscio et al. [34]
Vitamin E	Vitamin E, selenium	There is no evidence that vitamin E prevents dementia, or that it improves cognitive function in people with MCI or AD	Farina et al. [35]
Vitamins B	Methionine-synthase mediated conversion of homocysteine to methionine, antioxidant, nerve growth and repair	There is no adequate evidence of an effect of vitamins B on general cognitive function, executive function	Li et al. [36]
Acetyl-L-carnitine	Activity at cholinergic neurons, membrane stabilization and enhancing mitochondrial function	There is no evidence of benefit of improvement in cognition or functional ability	Hudson [37]

Agent	Proposed mode of action	Reason	Reference
Piracetam	Multiple complex mechanisms	The evidence does not support the use of piracetam in the treatment of people with dementia or cognitive impairment	Flicker and Evans [38]
Semagacestat	γ-Secretase inhibition	Serious adverse events (weight loss, skin cancers and infections), worsening of cognition and functioning	Doody et al. [39]
Tarenflurbil(R-flurbiprofen)	γ-Secretase inhibition	No effect on cognitive decline or the loss of daily living activities in mild AD	Green et al. [40]
Bapineuzumab	Humanized, N-terminal specific anti-Aβ monoclonal antibody	No significant improvement in cognition, serious side effects, vasogenic edema	Abushouk et al. [41]
Solanezumab	Humanized monoclonal IgG1 antibody directed against the mid-domain of the Aβ peptide	No significant improvement in cognition	Honig et al. [42]

Table 1.
The anti-AD drug candidates for which the clinical trials have been failed or suspended.

in AD, measuring cognitive abilities is a reductionist approach as the disease is too complex and transgenic animal models are not capable of mimicking the various pathophysiological mechanisms in humans. Several new chemical entities claiming to have potential benefits in AD have been developed by researchers all over the globe. However, the evolution of a definite disease modifying therapy for AD is constantly under the threat of chasing the wrong pathology [22].

4. Ongoing clinical trials for Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder resulting from progressive pathological changes characterized by protein deposits in the form of amyloid plaques (APs) and neurofibrillary tangles (NFTs), which cause synaptic and neuronal loss. According to generally accepted hypothesis AD starts with abnormal processing of amyloid precursor protein (APP) [2]. Excess production or reduced clearance of β-amyloid peptide monomers, which is produced by the amyloidogenic cleavage of the membrane-spanning protein APP are the two main mechanisms of this abnormal deposition process, which causes aggregation of β-amyloid (Aβ) fibrils in extracellular APs. Second core pathophysiological mechanism of the disease is the intraneuronal deposition of hyperphosphorylated tau (pT) within NFTs [5].

Synaptic dysfunction, mitochondrial and oxidative changes, neuroinflammation, gliosis, and finally apoptosis and neuronal loss are known neurodegenerative consequences of AD, which are reflected in the macroscopical level as the regional cortical atrophy starting from limbic regions of the brain and then traveling trans synaptically to paralimbic, heteromodal and finally to unimodal association cortices. These changes and dysfunctions of the neurotransmitter systems such as acetylcholine, serotonin, glutamate, noradrenaline, dopamine cause clinical manifestations.

All these pathological changes are the targets of ongoing clinical trials for the treatment of AD. The term "disease-modifying strategies in AD" primarily connotes

treatment strategies aiming at the prevention of and/or clearance of pathological Aβ and tau. Neurotransmitter-based strategies and others, such as combatting against oxidative stress or neuroinflammation are generally classified as "symptomatic treatments". In this section, current disease-modifying and symptomatic treatment strategies will be reviewed.

4.1 Amyloid-focused ongoing clinical trials

According to the amyloid cascade hypothesis, AD begins with the accumulation of Aβ, years before its clinical onset. APP is a transmembrane protein whose physiological function is not completely understood. In a healthy brain, APP is metabolized by three proteolytic enzymes, namely α, β and γ secretases [43]. Proximally, γ-secretase cleaves the protein in its membrane-spanning domain solely by itself, forming an intracellular carboxy-terminal fragment (CTF), which is probably pro-plastic by translocating into the neuronal nucleus and playing a role in pro-plastic signaling. However distally, APP is cleaved alternatively, either by α-secretase or by β-secretase (BACE) on its two different sites in the extracellular domain close to the amino terminal of APP. The former cleavage is non-amyloidogenic since it produces an inert peptide called p3 in the mid-segment and another one, which is called sAPPα containing the N-terminus and probably having some neurotrophic functions. However, the latter cleavage is amyloidogenic, since it produces the anti-plastic and deposition-prone Aβ fragment in the mid-segment and sAPPβ in the N-terminus. The resulting Aβ will either be cleared by lysosomal-proteasomal mechanisms or will oligomerize and start to induce its pathophysiological functions. Now it is known that soluble oligomers of Aβ are more toxic than its more downstream moieties that are insoluble protofibrils and fibrils [44, 45].

Therefore, current studies aim to agonize α-secretase activity (ADAM10 activators), inhibit β-secretase (BACE inhibitors), and inhibit or modulate γ-secretase (GSIs and GSMs). Also enhancing clearance of Aβ with active or passive immunotherapies or prevention of aggregation of APs are the treatment focuses of ongoing trials. Monoclonal antibodies bind different epitopes which are N-terminal, C-terminal or mid-domain of Aβ and different conformations of Aβ which are monomer, oligomer and fibril [46].

4.1.1 Reducing Aβ production

Two secretases, namely α and γ are seemingly no longer the focus of drug development efforts for AD, as a result of many failures in clinical trials and concerns that their interaction with other substrates may trigger diseases like cancer. Specific ADAM10 activators that will act only in the brain thus preventing its potential role in breast cancer is yet to be developed [47] In a recent review it was stated that "the future of γ-secretase inhibition as an AD treatment strategy may depend on the development of GSMs, which aim to cause a shift from Aβ1-42 species toward the shorter and less pathogenic forms of Aβ, while also sparing Notch" [48].

β-Secretase is an aspartic acid protease belongs to the pepsin family. β-Site APP cleaving enzyme 1 (BACE1) plays role in Aβ production. BACE1 inhibition strategies do not share the same concerns for interfering with the other secretases. Therefore BACE1 inhibition is one of the strategies to interfere with amyloid cascade. There are ongoing trials with E 2609 (NCT03036280, NCT02956486), CNP520 (NCT02565511, NCT03131453) and JNJ-54861911 (NCT02569398, NCT01760005) [49].

4.1.2 Aβ clearance

The first experience of active vaccine trial was with AN1792 and ended occurrence of T-cell mediated meningoencephalitis [50]. Now the only ongoing active vaccine trial is CAD-106 that generates anti-Aβ antibodies to N-terminus [51, 52].

Crenezumab is a humanized IgG4 monoclonal antibody (mAb) that binds the mid-domain of the Aβ peptide (residues 13–24) and binds multiple conformations of Aβ (monomers, oligomers, fibrils) [53, 54]. Patients with mild to moderate Alzheimer Disease and also Preclinical Presenilin1 (PSEN1) E280A Mutation Carriers are involved in ongoing trials of Crenezumab (NCT03491150, NCT03114657, NCT02353598, NCT01998841, NCT02670083).

Gantenerumab is a first fully human IgG1 mAb binds an N-terminal [3–12] and central [18–27] amino acids of the Aβ peptide. It binds monomers weaker than oligomers and fibrils [46]. Gantenerumab is being evaluated in phase 2 and 3 trials in individuals with prodromal and early AD and individuals at risk for and with early-stage autosomal-dominant AD (NCT02051608, NCT03444870, NCT03443973, NCT01224106, NCT01760005) [46, 55, 56].

Aducanumab is a fully human IgG1 mAb binds the N-terminus (residues 3–6) of Aβ peptide. It recognizes oligomers and fibrils but it does not react to the monomers [18]. Ongoing Aducanumab trials involve prodromal, early and mild AD patients (NCT03639987, NCT02484547, NCT02477800, NCT01677572) [46, 57].

Solanezumab is a humanized IgG1 mAb, binds the mid-domain of Aβ (residues 16–26). It specifically recognizes monomers [58]. There are two ongoing prevention trials with solanezumab (NCT01760005, NCT02008357).

4.1.3 Other anti-amyloidogenic compounds

In addition to abovementioned strategies, there are some other anti-amyloidogenic compounds with diverse mechanisms. ALZT-OP1 prevents Aβ aggregation and neuroinflammation and is being evaluated in phase III clinical trial (NCT02547818) [59]. Posiphen is another anti-amyloidogenic drug that currently in phase I/II clinical trial (NCT02925650) [60].

Update of selected anti-Alzheimer's disease drugs in clinical trials including anti-amyloid strategies are summarized in **Table 2**.

4.2 Tau-focused ongoing clinical trials

Tau is a microtubule-associated protein (MAP) in neurons which regulates the axonal transport [63]. Although tau pathology proved to be more correlated with clinical symptoms than amyloid mechanisms, tau-based therapeutic strategies are relatively new. Beta-folded oligomers of abnormal phosphorylation of tau are the main component of NFTs. Post-translational modifications such as phosphorylation, acetylation and truncation play a major role in tau function [64]. Modulating tau phosphorylation, targeting other tau post-translational modifications, microtubule stabilizers, tau aggregation inhibitors, anti-tau immunotherapy are the mechanisms targeted by clinical trials. Current clinical trials focusing on tau are summarized in **Table 3**.

4.2.1 Targeting tau-post-translational modifications

Salsalate is a nonsteroidal anti-inflammatory drug that has been shown to inhibit acetyltransferase p300-induced tau acetylation in frontotemporal dementia (FTD) mouse model [75]. There is a phase I clinical trial in patients with prodromal to mild

Target	Drug name	Study title	Therapy type	Trial status	Company	Clinical trial identifier
BACE inhibitor	E2609 Elenbecestat [49]	A 24 Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease_ (MissionAD2)	Small molecule	Phase III	Biogen, Eisai Co., Ltd.	NCT03036280
		A 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease_ (MissionAD2)	Small molecule	Phase III	Biogen, Eisai Co., Ltd.	NCT02956486
	CNP520 [49]	A Study of CAD106 and CNP520 Versus Placebo in Participants at Risk for the Onset of Clinical Symptoms of Alzheimer's Disease	Small molecule	Phase II/III	Amgen, Inc., Novartis Pharmaceuticals Corporation	NCT02565511
		A Study of CNP520 Versus Placebo in Participants at Risk for the Onset of Clinical Symptoms of Alzheimer's Disease	Small molecule	Phase II/III	Amgen, Inc., Novartis Pharmaceuticals Corporation	NCT03131453
	JNJ-54861911 [49]	An Efficacy and Safety Study of Atabecestat in Participants Who Are Asymptomatic at Risk for Developing Alzheimer's Dementia (EARLY)	Small molecule	Phase II/III	Janssen, Shionogi Pharma	NCT02569398
		Dominantly Inherited Alzheimer Network Trial: An Opportunity to Prevent Dementia. A Study of Potential Disease Modifying Treatments in Individuals at Risk for or With a Type of Early Onset Alzheimer's Disease Caused by a Genetic Mutation.	Small molecule	Phase II/III	Janssen, Shionogi Pharma	NCT01760005
Aβ clearance	CAD106 [49, 61]	A Study of CAD106 and CNP520 Versus Placebo in Participants at Risk for the Onset of Clinical Symptoms of Alzheimer's Disease	Active immunotherapy	Phase II/III	Novartis Pharmaceuticals Corporation	NCT02565511
	Crenezumab	An Open-Label Crenezumab Study in Patients with Alzheimer's Disease	Passive immunotherapy	Phase III	Hoffmann-La Roche	NCT03491150
		A Study of Crenezumab Versus Placebo to Evaluate the Efficacy and Safety in Participants with Prodromal to Mild Alzheimer's Disease (CREAD 2)		Phase III	Hoffmann-La Roche	NCT03114657

Target	Drug name	Study title	Therapy type	Trial status	Company	Clinical trial identifier
		A Study of Crenezumab Versus Placebo in Preclinical Presenilin1 (PSEN1) E280A Mutation Carriers to Evaluate Efficacy and Safety in the Treatment of Autosomal-Dominant Alzheimer's Disease, Including a Placebo-Treated Non-Carrier Cohort [27]		Phase II	• Genentech, Inc. • Banner Alzheimer's Institute • National Institute on Aging (NIA)	NCT01998841
		CREAD Study: A Study of Crenezumab Versus Placebo to Evaluate the Efficacy and Safety in Participants with Prodromal to Mild Alzheimer's Disease [20]		Phase III	AC Immune SA, Genentech, Hoffmann-La Roche	NCT02670083
	Gantenerumab	A Study of Gantenerumab in Participants with Mild Alzheimer Disease	Passive immunotherapy	Phase III	Hoffmann-La Roche	NCT02051608
		A Study of Gantenerumab in Participants with Prodromal Alzheimer's Disease [56]		Phase III	Hoffmann-La Roche	NCT01224106
		Dominantly Inherited Alzheimer Network Trial: An Opportunity to Prevent Dementia. A Study of Potential Disease Modifying Treatments in Individuals at Risk for or With a Type of Early Onset Alzheimer's Disease Caused by a Genetic Mutation. (DIAN-TU) [55]		Phase II Phase III	• Washington University School of Medicine, Eli Lilly and Company, Hoffmann-La Roche (and 5 more)	NCT01760005
	Aducanumab	A Study of Aducanumab in Participants with Mild Cognitive Impairment Due to Alzheimer's Disease or With Mild Alzheimer's Disease Dementia to Evaluate the Safety of Continued Dosing in Participants with Asymptomatic Amyloid-Related Imaging Abnormalities	Passive immunotherapy (against aggregated Aβ)	Phase II	Biogen	NCT03639987
		221AD302 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease (EMERGE) [46]		Phase III	Biogen	NCT02484547

Target	Drug name	Study title	Therapy type	Trial status	Company	Clinical trial identifier
		21AD301 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease (ENGAGE) [46]		Phase III	Biogen	NCT02477800
		Multiple Dose Study of Aducanumab (BIIB037) (Recombinant, Fully Human Anti-Aβ IgG1 mAb) in Participants with Prodromal or Mild Alzheimer's Disease (PRIME) [57]		Phase I	Biogen	NCT01677572
	Solanezumab	Dominantly Inherited Alzheimer Network Trial: An Opportunity to Prevent Dementia. A Study of Potential Disease Modifying Treatments in Individuals at Risk for or With a Type of Early Onset Alzheimer's Disease Caused by a Genetic Mutation. (DIAN-TU) [55]	Passive immunotherapy (against Aβ3–12 and Aβ18–27)	Phase II Phase III	• Washington University School of Medicine • Eli Lilly and Company • Hoffmann-La Roche (and 5 more)	NCT01760005
		Clinical Trial of Solanezumab for Older Individuals Who May be at Risk for Memory Loss [62]		Phase III	• Eli Lilly and Company • Alzheimer's Therapeutic Research Institute	NCT02008357
Other Anti-amyloidogenic Compounds	ALZT-OP1 [59]	Safety and Efficacy Study of ALZT-OP1 in Subjects with Evidence of Early Alzheimer's Disease (COGNITE)		Phase III	AZTherapies, Inc.	NCT02547818
	Posiphen® [60]	Safety, Tolerability, PK and PD of Posiphen® in Subjects with Early Alzheimer's Disease (DISCOVER)		Phase I Phase II	• QR Pharma Inc. • Alzheimer's Disease Cooperative Study (ADCS)	NCT02925650

Table 2.
Update of selected anti-Alzheimer's disease drugs in clinical trials including anti-amyloid strategies.

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Target	Drug name	Study title	Therapy type	Trial status	Company/sponsor	Clinical trial identifier
Lisin acetylation inhibitor	Salsalate [65]	Salsalate in Patients Mild to Moderate Alzheimer's Disease	Small molecule	Phase I	Adam Boxer	NCT03277573
c-Abl inhibitor	Nilotinib [66]	Impact of Nilotinib on Safety, Biomarkers and Clinical Outcomes in Mild to Moderate Alzheimer's Disease	c-Abl inhibitor	Phase II	Georgetown University	NCT02947893
Microtubule stabilizers	TPI-287	A Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Preliminary Efficacy Study of TPI-287 in Alzheimer's Disease	Small molecule	Phase I	Cortice Biosciences	NCT01966666
Tau aggregation inhibitors	TRX-0237 [67, 68]	Safety and Efficacy of TRx0237 in Subjects with Early Alzheimer's Disease	Small molecule	Phase II-III	• TauRx Therapeutics Ltd	NCT03446001
	Nicotinamide	Nicotinamide as an Early Alzheimer's Disease Treatment (NEAT)	Lysosomal acidification	Phase II	• University of California, Irvine	NCT03061474
Anti-Tau immunoteraphies	AADvac-1 [67]	24 Months Safety and Efficacy Study of AADvac1 in Patients with Mild Alzheimer's Disease	Active immunotherapy	Phase II	Axon Neuroscience SE	NCT02579252
	ACI-35 [19]	A study comparing the safety and effects of a new compound, ACI-35 with placebo in patients with mild to moderate Alzheimer's disease	Active immunotherapy	Phase I	AC Immune SA, Janssen	ISRCTN13033912
	IvIg [69–71]	Study of Intravenous Immunoglobulin in Amnestic Mild Cognitive Impairment	Active immunotherapy	Phase II	• Sutter Health	NCT01300728
		A Study to Evaluate Albumin and Immunoglobulin in Alzheimer's disease	Active immunotherapy	Phase II Phase III	Instituto Grifols, S.A./ Grifols Biologicals Inc.	NCT01561053
	ABBV-8E12 [72, 73]	A Study to Evaluate the Efficacy and Safety of ABBV-8E12 in Subjects with Early Alzheimer's Disease	Passive Immunotherapy	Phase II	AbbVie	NCT02880956
		An Extension Study of ABBV-8E12 in Early Alzheimer's Disease	Passive Immunotheraphy	Phase II	AbbVie	NCT03712787
	RO 7105705 [74]	A Study to Evaluate the Efficacy and Safety of RO7105705 in Patients with Prodromal to Mild Alzheimer's Disease	Passive Immunotheraphy	Phase II	Genentech, Inc	NCT03289143

Table 3.
Current clinical trials focusing on tau.

AD (NCT03277573). Nilotinib is a c-Abl tyrosine kinase inhibitor used in patients with leukemia [76]. It is thought to clean tau by inducing autophagy. It is being evaluated in a phase II clinical trial in patients with mild to moderate AD (NCT02947893).

4.2.2 Microtubule stabilizers

TPI-287 is a small molecule that stabilizes microtubules. It is tested in a phase I clinical trial in AD patients [77].

4.2.3 Tau aggregation inhibitors

LMT-X or named as TRx0237 is a second generation formulation of methylene blue that targets tau accumulation [77]. There is a phase II/III clinical trial in patients with early AD (NCT03446001) [67, 68]. Nicotinamide is the precursor of coenzyme Nicotinamide adenine dinucleotide prevents phosphorylation of tau in mice. A phase II study in mild-to-moderate Alzheimer's disease is currently ongoing (NCT03061474).

4.2.4 Active immunotherapy

There are three active immunotherapy agents being evaluated in ongoing trials. AADvac-1 contains synthetic tau peptide spanning residues 294–305 derived from a naturally occurring truncated and misfolded tau protein coupled to keyhole limpet hemocyanin and aluminum hydroxide as adjuvant [77]. A phase II clinical trial in subjects with mild AD is ongoing (NCT02579252) [78]. ACI-35 is a synthetic peptide spanning the human protein tau sequence 393–408, phosphorylated at S396 and S404 [72]. A phase I clinical trial in subjects with mild to moderate AD is ongoing (ISRCTN13033912) [19]. Intravenous immunoglobulin (IVIg) is a human plasma-derived product consisting of polyclonal serum IgG used as anti-inflammatory and immunomodulatory therapy for various neurological diseases [73]. There are phase II and III studies in subjects with mild cognitive impairment and AD (NCT01300728, NCT01561053) [69, 70].

4.2.5 Passive immunotherapy

ABBV-8E12 is a humanized anti-tau monoclonal antibody. There are two studies with ABBV-8E12 in patients with early AD (NCT02880956, NCT03712787) [72, 73]. Another passive immunotherapy agent R07105705 is an anti-tau antibody [39]. It is being evaluated in patients with prodromal to mild AD (NCT03289143) [74].

4.3 Other ongoing clinical trials

Riluzole, a sodium channel blocker, is used as a disease-modifying drug for amyotrophic lateral sclerosis [79]. It lowers extracellular glutamate levels, inhibits presynaptic glutamate release and induces glutamate transporter activity. Riluzole is being evaluated in a Phase II clinical trial in patients with mild AD (NCT01703117) [79–82].

LMA11A-31 is a small molecule prevents synaptic dysfunction, spine loss, neurite degeneration, microglial activation, and cognitive deficits in animal models [83, 84]. A phase I/II trial with mild to moderate AD patients is ongoing (NCT03069014) [85]. AD is thought to be linked with viral infections [86, 87]. Therefore a phase II trial is ongoing in mild AD patients who test positive for serum antibodies for herpes simplex virus 1 or 2, with valacyclovir (NCT03282916). Lifestyle interventions, management of metabolic and cardiovascular risk factors,

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Target	Drug name	Study title	Therapy type	Trial status	Company	Clinical trial identifier
Glutaminergic	Riluzole [79–82]	Riluzole in Mild Alzheimer's Disease	Small molecule	Phase II	Sanofi	NCT01703117
Neurotrophins and Their Receptor-based Therapies	LM11A-31-BHS [85]	Study of LM11A-31-BHS in Mild–moderate AD Patients		Phase I Phase II	• PharmatrophiX Inc. • National Institute on Aging (NIA)	NCT03069014
Therapies Targeted at Neuroinflammation and Oxidative Stress	Valacyclovir [85]	Anti-viral Therapy in Alzheimer's Disease		Phase II	New York State Psychiatric Institute National Institutes of Health (NIH) National Institute on Aging (NIA)	NCT03282916
Therapies and Interventions for AD Prevention	Insulin (Humulin R® U-100) [85]	The Study of Nasal Insulin in the Fight Against Forgetfulness (SNIFF)		Phase II Phase III		NCT01767909

Table 4.
Other strategies of Alzheimer's disease treatment.

exercise and diet are the focuses for primary prevention of AD (NCT01767909, NCT03249688) [88–92].

Deep brain stimulation is a novel therapeutic strategy for AD. One trial is ongoing in patients with mild AD (NCT03622905). Other strategies of Alzheimer's disease treatment are summarized in **Table 4**.

5. Gene and stem cell therapy in Alzheimer disease

5.1 Genetics of Alzheimer's disease

Both age and family history are important risk factors for AD. The risk of developing AD increases for one who has a first-degree relative with AD when compared to the general population. AD can be grouped into two subtypes with respect to age of onset. Most of the AD cases (>95%) are late-onset AD (sporadic/LOAD) (above age 65) that is considered to be multifactorial [93]. Many susceptibility genes for LOAD have been defined thanks to genome-wide association studies (GWAS) and several other sequencing analyzes. For instance, one of the well-studied genetic risk factors for LOAD is an alteration in Apolipoprotein E (APOE) coded by the gene localized to 19q13 [94]. APOE is a multifunctional protein which serves a number of functions in neuronal activities. In brain tissue, there are three main isoforms that are diversified by each other by different one amino acid, which are APOEε2 (Cys112, Cys158), APOEε3 (Cys112, Arg158) and APOEε4 (Arg112, Arg158). The differences between these three APOE isoforms have a significant impact on the structure and function of APOE at molecular and cellular levels. Therefore, those are thought as associated with neuropathological conditions [95].

Early onset AD (Familial/EOAD) represent <5% of all cases of AD. APP (Amyloid beta (A4) precursor protein), PSEN1 (Presenilin 1), and PSEN2 (Presenilin 2) genes mutations are exclusively considered as a basis for EOAD in most cases [94]. APP, a transmembrane protein in neuron cells, is cleaved by β-secretase and γ-secretase, respectively, to produce β-amyloids (Aβ) and some other side products [96]. Since neurotoxic consequences of altered Aβ ratios like neurodegeneration resulting from aberrant synaptic function take place in brain, APP mutations have continuously been investigated. Yet, only approximately 15% of EOAD could be enlightened by dominant APP gene mutations [97].

Another protein that is strictly associated with the progression of AD is PSEN1 as it is the principal component of γ-secretase complex. Since neurotoxic fragments are formed by proteolytic function of γ-secretase on APP, PSEN1 gene mutations give rise to abnormal activity of the proteolytic enzyme leading to abnormal or longer Aβ fragments and, therefore this contributes to development of EOAD [95]. More than 180 autosomal dominant PSEN1 mutations associated with AD have been reported, which makes PSEN1 significantly important protein in the occurrence of EOAD [98]. Disease-causing PSEN1 gene mutations, showing complete penetrance, accounts for majority of EOAD (approximately 80%) and these mutations are defined as the most common cause of the disease [99]. Lastly, the gene PSEN2 is also coding for one subunit of γ-secretase, the aspartyl protease generates Aβ. Missense mutations are reported in PSEN2, which are rarely genetic basis of EOAD [100]. In total, as mentioned in Zou's review article in 2013, majority of the disease-causing mutations identified for the EOAD have been reported in PSEN1 gene (approximately 78%), followed by APP mutations (17%) then with rare PSEN2 gene mutations (approximately 5%) [94].

Technological advances in sequencing methods over the past decade allow researchers to investigate AD thoroughly, especially genetic fundamentals of the

disease. Since high-throughput sequencing provides a large number of polymorphisms in numerous subjects, new several genes associated with AD risk have been emerged and reported [96]. Accordingly, genome-wide association studies (GWAS) about AD increased, which consequently suggests new gene therapy strategies.

5.2 Gene therapy for AD

Discovering risk loci by GWAS studies may help to enlighten the biological mechanisms underlying AD because the reported genes might have been target for medicines, thereby this issue promises further investigation in order to improve gene therapy strategies and thus precision medicine concept for AD [101].

Over time, gene delivery of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), APOE, ECE (endothelin-converting enzyme) have been investigated in several animal models of AD. Endothelin-converting enzyme (ECE) is protease involved in the degradation of Aβ peptides. Intracranial administration of five recombinant adeno-associated viral vector (rAAV) containing the ECE-1 synthetic gene showed reduced Aβ in the anterior cortex and hippocampus in APP-PS1 transgenic mice. Use of AAV vector encoding anti-Aβ Ab in Tg2576 mice results in a significant decrease in Aβ level in the brain of subjects. These results support its use for the prevention and treatment of AD [102].

The first clinical trial using Adeno-Associated Virus delivery of NGF has been accomplished and the results indicate amelioration of AD pathogenesis. Clinical trials were conducted using CERE-110 that is an AAV2/2 vector containing full length NGF transgene for the treatment of AD patients. These trials confirmed that AAV2-NGF delivery was well tolerated with a high level of safety and no systemic toxicity but did not affect clinical outcomes or selected AD biomarkers (NCT00087789, NCT00876863) [103].

5.3 Stem cell treatment for AD

Stem cells (SCs) are continuously capable of self-renewing and differentiating into specialized cells. Accordingly, SC therapy is surely becoming a promising strategy in the treatment of neurodegenerative diseases including AD owing to the capacity of SCs to migrate and reach areas of the brain. SCs are classified into four groups; embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cell, and neural stem cells [104].

5.3.1 Embryonic stem cells (ESCs)

ESCs, called as pluripotent, are derived from the inner cell mass of blastocyst because they have the ability to develop cell types from the ectoderm, mesoderm, and endoderm germ layers [105]. ESCs may an excellent cell replacement therapy approaches for transplantation in AD [104]. In vitro studies have been successful to differentiate ESCs into specific neuronal cell types like dopaminergic neurons and these studies show that the role of ESCs and their derivatives reduce AD pathology in rodent models [106, 107].

Several studies reveal that ESC-derived NSCs can be safely transplanted without tumorigenesis despite the fact that undifferentiated ESCs have risks of tumor formation, transplantation rejection and immune responses [106, 108, 109]. Experiments conducted on human ESCs have been able to generate dopaminergic neurons, spinal motor neurons and astroglial cells [110]. Some studies demonstrated use of retinoic acid (RA) induce direct differentiation of human ESCs into basal forebrain cholinergic neurons (BFCNs). Tang et al. showed that ESC-derived

NPC transplantation into an Aβ-injured rat model improves memory impairment compared to sham controls [106].

5.3.2 Induced pluripotent stem cells (IPSCs)

Induced pluripotent stem cells could be generated from adult cells by the overexpression of key transcription factors (OCT4, SOX2, KLF4, LIN28, and NANOG) [111, 112]. iPSCs are in general similar to embryonic stem cells (ESCs) in morphology, gene expression profile and potential of differentiation [113].

Human iPSCs derived from AD patients' somatic cells can provide a new perspective to develop new strategies for disease modeling. Yagi et al. showed that fAD-iPSC-derived differentiated neurons have increased amyloid β42 secretion, responds to γ-secretase inhibitors and modulators, indicating the potential for identification and validation of candidate drugs [114]. Takamatsu et al. used iPSCs to derive macrophage-like myeloid lineage cells that could express neprilysin which is a protease with Aβ-degrading activity [115].

Recent studies have shown reprogramming structural chromosomal abnormalities and aberrant DNA methylation patterns in hiPSCs [116]. iPSCs can be edited by gene editing technologies like recombinant homologous, transcription activator-like effector nucleases (TALENs), clustered regularly interspaced short palindromic repeats (CRISPR-cas9) and can function as more suitable for cell transplantation.

5.3.3 Mesenchymal stem cells (MSCs)

Mesenchymal stem cells (MSCs) are adult multipotent progenitors and can be obtained from various adult tissues including bone marrow, peripheral blood, umbilical cord, adipose tissue, amniotic fluid. MSCs are most favored cell types in the treatment of AD due to their accessibility, relative ease of handling, secretion of a wide range of cytokines, easily transplanted intravenously into patients, and lack of ethical issues.

Most important features of ESCs is a wide range of differentiation potentials including neuronal cells [110]. Park et al. reported that transplanted human adipose tissue derived mesenchymal stem cells (ADMSCs) differentiate into neural cells in the brain and these cells can restore cognitive functions of mice by increasing acetylcholine synthesis, brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and restoring neuronal integrity [117]. In addition, MSC transplantation has been shown to inhibit Aβ and tau-related cell death, and to reduce Aβ residues and plaque formation by modulating neuroinflammation [118, 119]. It has been reported that bone marrow-derived mesenchymal stem cells provide a reduction in Aβ deposits and facilitate changes in key proteins required for synaptic transmissions such as dynamin 1 and synapsin 1 [120].

5.3.4 Neural stem cells (NSCs)

Transplantation of growth factor-secreting NSC was reported to increase neurogenesis and cognitive function in a rodent AD model [121]. And the overexpression of NSC derived cholinergic neurons restored cognitive performance and synaptic integrity in a rodent model [122].

6. Conclusion

Alzheimer's disease is a progressive neurodegenerative disease that affects the central nervous system. Many complex pathological and genetic features have been

described in the disease. Aβ aggregation, tau aggregation, metal dyshomeostasis, oxidative stress, cholinergic dysfunction, inflammation and downregulation of autophagy based on pathophysiological changes occur during the onset and progression of AD have been proposed. There is no effective treatment currently, however, at present, current drug treatments of AD, such as cholinesterase inhibitors or NMDA antagonists, mainly help to manage symptoms hereby obviating the need for new approaches to deal with AD underlying mechanisms. Ongoing advances in the knowledge of pathogenesis, in the identification of novel targets, in improved outcome measures, and in identification and validation of biomarkers may lead to effective strategies for AD prevention.

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