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REVIEW ARTICLE

Alzheimer's Disease: Potential Targets and Newer Monoclonal Antibodies

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ABSTRACT
Alzheimer's disease (AD) is a complex neurodegenerative disease, affecting a significant part of the population. Neuropathological hallmarks are β-amyloid (Aβ) plaques and neurofibrillary tangles, but cholinergic hypothesis and oxidative hypothesis also have a fundamental role in the pathogenesis of AD. The enormous challenge that AD possesses to global healthcare makes it as urgent as ever for researchers to develop treatment strategies to fight this disease. Thus, potential targets are aimed at Tau aggregation, mitochondria, inflammation and insulin resistance, oxidative stress, MAPK signaling, ApoE4, plasmalogens. The present review provides an insight into the different molecular mechanisms involved in the development and progression of the AD and potential therapeutic targets along with the new drugs recently approved by the US FDA for the specific targets.
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INTRODUCTION

The disease was first described by Dr. Alois Alzheimer, in 1906. Nowadays Alzheimer's disease has been the most common cause of dementia in aged individuals [1]. Cellular and molecular events trigger neural dysfunction that provokes neurotoxicity and neural death. According to the latest statistics available from the World Health Organization, around 47 million people have dementia. The total number of people with dementia is projected to near 75 million in 2030 and almost triple to 115 million by 2050 [2,3]. Irrevocable loss of neurons, mainly in the cortex and hippocampus results in Alzheimer's disease which is a progressive neurologic disease. The manifestations are progressive impairment in memory, judgment, decision making, orientation to physical surroundings, and language [4]. The chronic progression of Alzheimer's disease is characterized by loss of memory and cognitive deficits such as agnosia, aphasia, and apraxia, and causes interference in daily life activities and in doing individual work and it is recognized that the risk of this disease is doubling every 5 years [5]. Neuropathologic hallmarks of AD are the presence of intracellular neurofibrillary tangles and extracellular Aβ plaques. Aβ is formed due to the splitting of amyloid precursor protein [APP] during the formation of the plaques in AD. Another big part of Alzheimer's disease is neurofibrillary tangles which consist of tau[τ] protein. Neurons are held together by their cytoskeleton, partly made up of microtubules these structures essentially act like minecarts shipping nutrients, vesicles, mitochondria, and chromosomes from the cell body to the ends of the axon and rearwards. The enzyme kinase transfers phosphate groups to the tau protein and hence tau becomes hyperphosphorylated. When this phosphate group binds tau protein, the tau protein clumps up with other tau proteins and forms tangled threads [1]. Although other relevant pathogenesis mechanisms have received more research attention in recent years. The goal of this review is to characterize the molecular mechanisms involved in Alzheimer's disease. The review also addresses potential targets or markers and their relevance to treatment. We aim to demonstrate the enduring value of various drugs in pharmacological therapy of Alzheimer's disease, especially newer monoclonal antibodies that may affect disease progression.

APPROACHING POTENTIAL ALZHEIMER'S DISEASE TARGETS

Tau aggregation: Lasagna-Reeves and his colleagues did a review on Tau Oligomers as Potential Targets and stated that easing of tau hyperphosphorylation using inhibitors of tau kinases, pharmacological balancing of microtubule networks by microtubule-binding drugs, activation of proteolytic or degradation pathways, and immunotherapy could be good approaches for tau oligomers [8]. Some of the authors also reviewed that by approaching to identify organic compound regulating the biological process of the same [9,10].

Mitochondria: Mitochondria are called as powerhouse of cells as it provides energy for carrying out vital functions like bioenergetics processes, intracellular calcium regulation, alteration of reduction-oxidation potential of cells, free radical scavenging, and activation of caspase-mediated cell death. In Alzheimer's disease, some mitochondrial dysfunction happens due to the progressive deposition of Amyloid-beta (Aβ). As amyloid-beta gets accumulated in extracellular as well as in different subcellular regions including endoplasmic reticulum, the Golgi apparatus, the early, late, or recycling endosomes, and the lysosomes. One of the well-established features of Alzheimer's disease is the alteration of energetic pathways. Positron emission tomography is used to measure glucose uptake in the brain and has shown a low rate of glucose metabolism in the regions like the hippocampus, posterior cingulate, temporal, and parietal lobes. Since we are relating reduction of glucose consumption as one of the features of the disease. This malfunction could be easily linked to mitochondrial dysfunction. In line with that, the critical remarks contributing to AD pathology is the altered balance between fusion and fission that interferes with mitochondrial transport contributes actively to the AD pathogenesis and these mitochondrial dynamics impairment could be a new therapeutic target in AD. Another paper showed impaired mitochondrial biogenesis in AD [11,12,13,14].

In line with other studies, mitochondrial dysfunction has come up as a crucial factor in AD. Although some other studies suggested a decrease in mitochondrial activity happens during aging and may get worse at the early stages of the disease, which contributes to its onset [11]. Although clinical trials showed failures due to some missing loops, the further evolution in understanding the disease and finding the key to drawbacks is going on. This could be one of the potential targets for treating Alzheimer's disease.

Inflammation and Insulin resistance: Angeles Vinuesa et al., did a review on inflammation and insulin resistance as risk factors for AD. Changes in metabolic function can lead to the risk of premature brain aging and the development of neurodegenerative disorders such as Alzheimer's disease. The various therapeutic approaches they studied were:

1. Insulin Signaling-Based Approaches like Intranasal Insulin, Glucagon-like peptide 1 receptor Analogs (GLP-1 Ras), Metformin, PPAR Agonists.
2. Inflammation-Based Approaches like TLR4 and Cytokine-Signaling Targeting, Non-steroidal Anti-inflammatory Drugs (NSAIDs), Liver X Receptor (LXR) Agonists and cholesterol Targeting.
3. Non-pharmacological Lifestyle Approaches like Physical Activity (PA), Diet, Microbiota Modulation are intended to highlight the therapeutic potential targets for AD. Apart from this they said lifestyle approaches can help to gear up different pathological elements as powerful preventive strategies. Therefore, this review aims and focuses on inflammation and insulin resistance as risk factors and therapeutic potential targets in Alzheimer's disease [15].

Oxidative stress: Oxidative stress is an imbalance between free radicals and antioxidants in the body. Reactive oxygen species have a useful role in host defense, gene transcription, regulation of synaptic plasticity, and apoptosis. However, the critical role of oxidative stress in the pathogenesis of the neurodegenerative disease is linked with various proteins such as α-synuclein, DJ-1, Amyloid-beta and tau protein, some signaling pathways like extracellular regulated protein kinases, phosphoinositide 3-Kinase/Protein kinase B pathway, and extracellular signal-regulated kinases ½, which are highly linked to neural damage. Tianfang Jiang et al., presented evidence on Oxidative stress as a potential therapeutic target of antioxidative agents in Alzheimer's disease by stating concerns regarding pathogenic proteins, their role in signaling pathways, and pathogenic mechanisms associated with oxidative stress in Alzheimer's disease. So, control and regulation of these proteins' functions and their signaling pathways can be a promising potential target to treat Alzheimer's disease [16].

Targeting MAPK Signalling: Guoxin Zu et al., conducted a study on "Mechanism of quercetin therapeutic targets for Alzheimer's disease by practicing a combination of network pharmacology with molecular docking simulations. They identified 263 candidate gene products potentially targeted by quercetin. For Alzheimer's disease, 9 gene products from OMIM, 143 from TTD, 218 from DisGeNET, GT from DrugBank, and 2712 from Gene Cards out of which 95 targets involved in the pathology of the disease. The common target identified for quercetin and AD was the MAPK signaling pathway because some of the biological process's components are linked to MAPK activity such as "kinase activity regulation", "cell proliferation", and "apoptosis". Some experts stated inhibition of MAPK expression in the hippocampus can significantly

improve memory, cognitive function, synaptic plasticity, and neuronal metabolism [17]. Therefore, by viewing all the positive input MAPK can be a therapeutic/core target for treating Alzheimer's disease.

Targeting Apolipoprotein (ApoE4)-An emerging therapeutic target: ApoE4 is the strongest genetic risk factor for Alzheimer's disease among its three polymorphic forms i.e, APOE2, APOE3, and APOE4. Mirna Safieh and colleagues studied ApoE4 as a therapeutic target for Alzheimer's disease. They studied the Role of ApoE4, the impact of the APOE genotype on other diseases, mechanisms involving apoE (Aβ metabolism, tau phosphorylation, transactive response DNA-binding protein 43 (TDP-43), lipid metabolism, mitochondrial function, neuroinflammation, vascular integrity/function, insulin, and VEGF signaling and synaptic plasticity. They suggested apoE4-directed therapeutic approaches should focus primarily on the apoE4 molecule and neutralize the effects of apoE4.

One more approach i.e, gene editing of APOE4 by CRISPR (Clustered regularly interspaced short palindrome repeats) was also practiced. Here the APOE4 gene is converted to either APOE3 or APOE2 which would lead to the abolition of the concentration difference between them may lead to ideal treatment.Here are some gleaned apoE4 protein directed approaches:

1. Reversal of hypo lipidation of apoE4
2. Anti-apoE4 immunotherapy
3. ApoE4 structural correctors
4. ApoE degradation
5. Molecules interacting with apoE4 and downstream signaling
6. ApoE-directed anti-amyloid treatment
7. ApoE receptor-related approach
8. ApoE mimetics
9. ApoE2-focused therapeutic approach
10. ApoE4 as a transcription factor
11. ApoE4 and inflammation
12. ApoE4 and vasculature [18].

Although the trials in humans have barely the results. Further advancement in the study can give a good approach and can be one of the potential therapeutic targets for treating Alzheimer's disease.

Plasmalogens: Plasmalogens are a subclass of phospholipids having a vinyl ether bond at the sn-1 position and an ester bond at the sn-2 position of the glycerol backbone. There are two types of plasmalogens, ethanolamine plasmalogens (PlsEtns) and choline plasmalogens (PlsChos). Mostly found in all mammalian tissues. The highest concentrations of plasmalogens are found in the brain, red blood cells, skeletal muscle, and spermatozoa. Plasmalogens constitute about 18-20% of the total phospholipids present in the cell membrane [20,21]. According to the study, the highest content of PlsEtns and PlsChos are found in the brain and heart muscle respectively from which PlsEtns constitute 30 mol% of the total phospholipids in the human brain [22,23,24]. Several types of research have focused on the plasmalogens replacement therapy in animals and reported promising outcomes. Intraperitoneal administration of purified plasmalogens for 7 days reduced the neuroinflammation in the hippocampus of adult male mice [27]. Oral administration of plasmalogens precursor PPI-1011 restored the reduced levels of plsEtns in plasma and brain and this was associated with stimulated remyelination of neuronal cells [26]. However, very minimal information is available on the therapeutic value of plasmalogens in humans, which suggests the need for further study [19]. The in vitro studies showed that plasmalogens strongly can reduce the activity of γ-secretase which is involved in the formation of Aβ peptides such as Aβ 40, Aβ 42, and Aβ 43 [27,28].

The study reported reduced Plsetns levels in plasma, serum, cerebrospinal fluid, and brain tissue in AD patients which suggests PlsEtns can be one of the potential candidates [19].

THE CURRENT LINE OF TREATMENTS

Donepezil [Aricept]: Synonyms: Aricept™, Donepezil Hydrochloride, Eranz®, E 2020. Chemical name of the drug is 2-[(1-benzylpiperidin-4-yl) methyl]-5,6-dimethyl-2,3-dihydroinden-1-one. This drug reversibly inhibits acetylcholinesterase (AchE), the enzyme that degrades the neurotransmitter acetylcholine after its release from the presynapse. Acetylcholinesterase inhibitors increase the availability of acetylcholine in cholinergic synapses, which enhances cholinergic transmission. Donepezil helps in delaying the process of progressive worsening of the cognitive symptoms of the disease. It is used for the conditions such as Alzheimer's disease, Dementia with Lewy Body, Down's Syndrome, and Parkinson's Disease Dementia. Donepezil is approved for Alzheimer's disease. US FDA status of Donepezil for Alzheimer's disease is approved. This drug is used to delay or slow the symptoms of mild to moderate AD. The common side effects reported are diarrhea, nausea, vomiting, dizziness, sleeplessness/fatigue, and urinary incontinence [29].

Galantamine: Synonyms: Razadyne™ , Reminyl™ , Nivalin®. Chemical name of the drug is (4aS. 6R, 8aS)-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6H-benzofuro [3a, 3, 2-ef][2] benzazepine-6-ol. This drug is targeted at the cholinergic system [28]. Galantamine, a cholinesterase inhibitor works with a dual mechanism of action. It reversibly inhibits acetylcholine esterase and also builds up the acetylcholine action on its receptors. This in turn increases cholinergic neurotransmission.[31] Galantamine is approved by U.S. FDA for Mild to Moderate Alzheimer's disease [30].

Memantine: Synonyms: Ebixa™, namenda™, Axura®, Akatinol®, Memary®The chemical name of the drug is 3,5-Dimethyl-1-adamantanamine. This is the only FDA-approved drug that is not an acetylcholinesterase inhibitor for the treatment of moderate to severe Alzheimer's disease [31]. This drug acts by blocking the flow through channels of NMDA receptor-operated ion channels, reducing glutamate effects [32,33]. The first combination drug trial to yield positive results for AD was Memantine and Donepezil in 2004 by Tariot et al. [34]

Rivastigmine: Synonyms: Exelon™, Rivastigmine tartrate, Rivastach®Patch, Prometax®, SDZ ENA 713.The chemical name of the drug is (S)-3-[1-(Dimethylamino)ethyl] phenyl N-ethyl-N-methylcarbamate. This drug is targeted at the cholinergic system. Rivastigmine reversibly inhibits acetylcholinesterase and butyrylcholinesterase enzymes and it is widely used to treat mild, moderate, and severe stages of Alzheimer's disease. This drug is also approved for mild to moderate dementia in Parkinson's Disease by US FDA [35].

NEWER MONOCLONAL ANTIBODIES:

Donanemab: Synonyms: - $N3_pG$-Aβ Monoclonal Antibody, LY3002813. Donanemab is also called $N3_pG$. It is humanized IgG1 monoclonal antibody. This monoclonal antibody is developed from mouse mE8-IgG2a. One characteristic feature of Alzheimer's disease is the presence of aggregated N-terminal pyroglutamate amyloid-beta(Aβ) epitope/Aβ(p3-42) in amyloid plaques formed in the brain [36,37]. The possible mechanism of donanemab is, that it targets the deposited Aβ(p3-42) in the brain lowers the targets and helps in reducing the load on the brain [18]. This drug donanemab has also overcome microhemorrhages one of the side effects of previously used plaque-binding antibodies. Another randomized preclinical study of combination therapy of N3pG with BACE inhibitor LY2811376 showed promising results in PDAPP-transgenic mice [36]. Although this fascinating drug is showing good results for AD still the trials are going on to make more data available so that it can be given as a treatment in the future to Alzheimer's disease patients.

Here below given a short summary of ongoing trials of donanemab. For more detailed information, see clinicaltrial.gov [38].

Clinical trials on LY3002813[donanemab]:

Drug Name	Sponser/Clinicaltrial.gov Identifier No	Mechanism of action	Enrollment	Characteristics	Status
LY3002813, Placebo	Eli Lilly and Company/ (NCT03367403)	Targets the deposited Aβ(p3-42) in the brain amyloid plaques	Estimated enrolment: - 266 participants of early symptomatic Alzheimer's disease.	Administered IV	Phase 2 Active, not recruiting, (TRAILBLAZER-ALZ)
LY3002813, Placebo	Eli Lilly and Company/ (NCT02624778)	Targets the deposited Aβ(p3-42) in the brain amyloid plaques	Actual enrolment: - 61 participants with mild cognitive impairment (MCI).	The drug is given as an intravenous infusion. It involves 3 parts Part A participants will receive a single dose of drug or placebo. Part B and part C will receive multiple doses of drug or placebo for 24 and 72	Phase 1 (completed)

				weeks respectively	
LY3002813	Eli Lilly and Company/ (NCT01837641)	Targets the deposited Aβ(p3-42) in the brain amyloid plaques	Estimated enrolment: - 100 participants with mild cognitive impairment due to Alzheimer's disease.	Drug given as intravenously and subcutaneously both.	Phase 1 (completed)
LY3002813, Placebo	Eli Lilly and Company/ (NCT05026866)	Targets the deposited Aβ(p3-42) in the brain amyloid plaques	Estimated enrolment: - 3300 participants with preclinical AD.	Donanemab and placebo are administered intravenously	Phase 3 Recruiting, (TRAILBLAZER-ALZ 3)
LY3002813, Placebo	Eli Lilly and Company/ (NCT04437511)	Targets the deposited Aβ(p3-42) in the brain amyloid plaques	Estimated enrolment: - 1800 participants with early symptomatic Alzheimer's disease (prodromal AD and mild dementia due to AD).	Donanemab and placebo are administered intravenously (IV)	Phase 3 Active, not recruiting, (TRAILBLAZER-ALZ 2)
LY3002813	Eli Lilly and Company/ (NCT05108922)	Targets the deposited Aβ(p3-42) in the brain amyloid plaques	Estimated enrolment: - 200 participants with Mild cognitive impairment and Alzheimer's disease.	Donanemab administered IV every 4 weeks. Aducanumab administered IV per label.	Phase 3, Recruiting, (TRAILBLAZER-ALZ 4)
LY3002813	Eli Lilly and Company/ (NCT04640077)	Targets the deposited Aβ(p3-42) in the brain amyloid plaques	Estimated enrolment: - 100 participants with conditions or diseases like Alzheimer's disease, dementia, brain disease, central nervous system disease, cognitive impairment.	It is in two arms Part A: - validation of remote scale assessments Part B: - Donanemab administered intravenously	Phase 2, Recruiting, (TRAILBLAZER-EXT)

Aducanumab [Approved for the treatment]:

In recent this new antibody Aducanumab (BIIB037), got approved to treat Alzheimer's disease. FDA granted accelerated approval along with marketing license on 7th June 2021. Aducanumab is a fully human

IgGI monoclonal antibody. Developed by Biogen and Neurimmune. It acts by crossing the blood-brain barrier and selectively targeting and binding aggregated Aβ plaques in the brain because of having a greater affinity for Aβ plaques. It is being available in single-dose vials for intravenous infusion administration. 170mg/1.7mL (100mg/mL), 300mg/3mL (100mg/mL). Dosing should be titrated till 10mg/kg i.e., seventh infusion onwards [39,40,41,42].

CONCLUSION

The vast majority of therapeutic strategies over the years are being focusing on reducing the major neuropathologic hallmarks of Aβ peptide in the brain. As described above, the Aβ cascade is considered the most prominent, the cholinergic hypothesis, tau, and oxidative hypothesis are equally important. There is no one particular reason for the disease, instead, all the pathogenesis pathways are interrelated which increases the possible severity of Alzheimer's disease. The recent drug treatment is only able to delay the process. Nowadays researches are in progress to address reducing the major challenging hallmark Aβ aggregated in the brain. Therefore, new monoclonal antibodies might be a promising candidate for AD pathogenesis and provide better therapeutics.

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