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Review Article

Emerging Treatment from novel targets for Alzheimer Disease

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ABSTRACT

Alzheimer disease (AD) is a neuropathological disease involving progressive neurodegeneration, initially impacting memory, and leading to progressive and irreversible cognitive decline and functional impairment. Tacrine was the first centrally acting cholinesterase drug discovered but was withdrawn because of hepatotoxicity. Currently there are four drugs being used for the treatment which includes donepezil, galantamine, rivastigmine, and memantine. The numerous complex and interrelated biochemical pathways underlying neurodegeneration in Alzheimer's disease provide numerous potential targets for therapeutic interventions. This review article is based on the various research findings done during the past two decades and will certainly help research scholar's to do further research in this field and will help in the development of drugs that will improve the quality of life of patients and will decrease care giver burden.

Keywords: Alzheimer Disease, Memantine, Tacrine

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INTRODUCTION

Dementia is a global issue involving 40 to 50 million people and the major contributor being Alzheimer disease especially in the elderly. It is the sixth leading cause of death in US. It was first discovered in the year 1907, when Dr. Alois Alzheimer described symptoms in patient known as Auguste Deter, who experienced memory loss, paranoia, and psychological changes. After her death, Dr. Alzheimer did autopsy and found shrinkage in and around nerve cells. He did microscopic investigation using new silver staining histological technique and observed the neuritic plaques, neurofibrillary tangles, and amyloid angiopathy which later became hallmark of disease and bear his name.[1]

Alzheimer disease (AD) is a neuropathological disease involving progressive neurodegeneration, initially impacting memory, and leading to progressive and irreversible cognitive decline and functional impairment. The most common cause of early onset neurodegenerative dementia is none other than EOAD (Early Onset Alzheimer Disease) contributing 4-6 % of all AD. EOAD has an incidence rate of about 6.3/100,000 and a prevalence rate of about 24.2/100,000 in the 45–64 year age group.[2]

Many factors such as diabetes, hypertension, smoking, obesity, and dyslipidemia have been associated with increased risk of AD, major factor being cerebrovascular disease. While all these increase the risk of Alzheimer disease, factors like higher educational attainment , consumption of omega-3 fatty acids, physical exercise reduce the risk of Alzheimer disease.[3]

The preclinical stage marks it onset with accumulation of Aβ and tau protein progressing to the stage of Mild cognitive impairment (MCI) marked by progressive episodic memory loss not affecting day to day functions and lastly overcome by the stage of dementia with progressive loss of functional abilities. Finally death ensues within 6-12 years of onset mainly due to pneumonia and pulmonary embolism as a result of immobility. Diagnosis is mainly based on use of biomarkers such as PET scan. Now there are FDA approved tracer's florbetaben, florbetabir and flutemetamol to detect AD pathology in Amyloid specific PET scan. [4]

CHOLINESTERASE INHIBITORS

AD is characterized by generalized cerebral cortical atrophy, neuronal loss, widespread cortical neuritic plaques and neurofibrillary tangles. The brain region most vulnerable to neuronal dysfunction and cell loss in AD is the medial temporal lobe, including entorhinal cortex and hippo- campus. Loss of Cholinergic neurons and cholinergic deficit is consistent and early finding in Alzheimer disease. Acetyl cholinesterase and butyrylcholinesterase are the two cholinesterases responsible for degradation of Ach, neurotransmitter involved in memory and learning.

Thus Acetyl cholinesterase Inhibitors (Ache I) have the potential therapeutic efficacy for symptomatic treatment of AD.[5] Out of four currently approved therapies for AD; Donepezil, Rivastigmine and galantamine are Ache I. Tacrine (1993) is the first centrally acting Anticholinesterase to be introduced for AD. It showed significant improvement in memory, attention, praxis, reason and language in many phase II and phase III trials. Later it was abandoned due to hepatotoxicity, gastrointestinal adverse reactions, poor oral bioavailability and frequent dosing requirements.[6]

Donepezil (1996) was approved for the treatment of mild-to-moderate AD. A twelve-week double-blind study with 468 AD patients divided into three groups: placebo, low dose (5 mg/day), and high dose (5 mg/day for week 1 and then 10 mg/day thereafter) was performed which showed significant improvement by the end of nine weeks. Donepezil not only block Cholinesterase Inhibitors but also block excitotoxic cascade induced by glutamate, mitigating the effects of oxidative stress, and reducing the expression of inflammation. Recently, for moderate-to-severe AD subjects, a higher dose of 23 mg was approved. [7] Rivastigmine (2000) has both BuChE and Acetyl cholinesterase inhibitory properties approved for the treatment of mild-to-moderate AD. A trial with 699 patients with mild to moderate AD was conducted. The patients were split into three groups: a placebo group, a group on 1–4 mg/day, and a group on 6–12 mg/day for 26 weeks. Patients in the 6–12 mg/day group demonstrated significant improvements in cognition (ADAS-cog 4.94 points), activities of daily living, global assessment of change, and the Mini-Mental State Examination (MMSE). Oral Rivastigmine has side effects such as nausea, vomiting, anorexia, and diarrhea. In 2007, to overcome GI side effects Rivastigmine transdermal patch was formulated. Galantamine (2001) was approved for the treatment of mild-to-moderate AD. It produces its action by nicotinic acetylcholine receptors. Galantamine in clinical trials showed significant improvement at daily doses of 16-32 mg for 3 to 6months duration. Galantamine is rapidly absorbed with absolute oral bioavailability between 80 and 100% and peak effect was achieved about one hour after a single oral dose of 8 mg .[8]

Huperzine A (1980), derived from the Chinese herb *Huperzia serrata*, is a potent, reversible, selective inhibitor of acetyl cholinesterase (Ache). 20 RCTs including 1823 participants showed a significant beneficial effect on the improvement of cognitive function as measured by Mini-Mental State Examination (MMSE) at 8 weeks, 12 weeks and 16 weeks, and by Hastgawa Dementia Scale (HDS) and Wechsler Memory Scale (WMS) at 8 weeks and 12 weeks.[9]

Phenserine is a non-competitive acetyl cholinesterase inhibitor. A double blind, 12 week study with two groups; one group receiving Phenserine (10 and 15 mg BID) and other receiving placebo were done. At 12 weeks, a non-statistically significant improvement on ADAS-cog scale for the high-dose Phenserine group was seen relative to placebo while it showed statistical significance if therapy was continued for more than 12 weeks.[10]

Ladostigil is a novel drug used in AD. It is neuroprotective and has Monoamine Oxidase and cholinesterase inhibitor activity. It prevented the age-related reduction in cortical Ache activity and the increase in butyrylcholinesterase activity in the hippocampus, in association with the reduction in gliosis. Currently it is in Phase II trials.[11]

N-methyl-D-aspartate (NMDA) receptor ANTAGONIST

N-methyl-D-aspartame (NMDA) receptors when acted upon by glutamate produce influx of Ca ions which through increasing free radicals and degrading protein and cell membrane produce cell death. Thus NMDA antagonists prevent neurons from excitotoxicity. Memantine, an NMDA antagonist is used in moderate to severe AD. A systemic review of double-blind, parallel-group, RCT studies of memantine showed improvement in cognition, ADL and behaviors in people with moderate to severe AD after 6 months of use.[12]

Aβ TARGETING THERAPIES

In AD, there is extracellular deposition of Aβ, a 40-42(3) amino acid polypeptide which lead to formation of senile plaques in the hippocampus. The Aβ is derived from a large transmembrane protein, the amyloid precursor protein (APP) by sequential proteolysis of two proteases, the β- and γ-secretase, at the N- and C-terminus of the Aβ sequence respectively. Alternatively, APP can also be processed by α-secretase within the Aβ sequence and thus not only preclude the formation of Aβ peptide but also generate a soluble neurotrophic sAPPα. Aβ is a neurotoxin; it aggregates and forms deposits that finally lead to neuronal dysfunction due to oxidative stress. Following this hypothesis, secondary prevention of AD can be made by: decreasing the production of Aβ, stimulation of clearance of Aβ formed or prevention of aggregation of Aβ into amyloid plaques.

BACE (β- site APP cleaving enzyme), Lateral ventricular injection of this inhibitor led to a significant dose- and time-dependent lowering of brain Aβ40 and Aβ42, a robust decreased sAPPβ and an increased sAPPα secretion. Another injection of KMI-429 into the hippocampus of APP transgenic mice reduced Aβ production. Oral administration of GSK188909 non-peptide BACE1 inhibitor results in a significant reduction in the level of Aβ40 and Aβ42 in brain.

DAPT-decreased Aβ levels in plasma and CSF. PMS777, a new cholinesterase inhibitor with anti-PAF activity, decrease sAPPα secretion and Aβ42 release in SH-SY5Y^{APP695} cells and PC12 cells while its effect on BACE1 inhibitors is still unclear.[13] γ- secretase inhibitors such as DAPT, BMS-299897 and MRK-560 decrease Aβ levels in plasma and CSF. Another γ- secretase inhibitors LY450139 dehydrate, decrease 38% plasma Aβ40 and 4.5% CSF Aβ40 in randomised controlled trial of 70 patients with mild to moderate Alzheimer disease. γ-secretase require notch for growth and development which produces side effects (e.g. severe gastrointestinal and haemopoetic side effects, neurodegeneration) which hamper development of clinically useful γ-secretase inhibitors.

Thus more focus is on development of γ-secretase modulator such as tarenflubril an NSAID, Phase III trials demonstrated that patients treated with it showed increased deterioration in cognition and activities of daily living compared to placebo-treated controls and it was discontinued. [14]Up regulation of α-secretase activity will decrease the amount of APP available for β-secretase, thereby decreased Aβ secretion and have therapeutic potential. Many studies had indicated that members of the adamalysin family of proteins ADAM (A Disintegrin and Metalloproteinase) mainly ADAM10, ADAM 17 and ADAM 9, fulfill some of the criteria required of α-secretase. Deprenyl increase α-secretase activity by promoting ADAM10 activity hence slows progression of AD. Intrahippocampal injection of iAβ5p a β- sheet breaker resulted in improved spatial memory and decreased amyloid plaque deposits. Tramiprosate binds to soluble Aβ and inhibits the formation of neurotoxic aggregates that lead to amyloid plaque deposition in the brain. M1 muscarinic receptors play a role in an apparent linkage of three major hallmarks of AD: Aβ peptide; tau hyperphosphorylation and loss of cholinergic function. Talsaclidine is a functionally selective muscarinic M1 agonist that stimulates non-

amyloidogenic α-secretase processing in vitro. Treatment with Talsaclidine decreased CSF Aβ about 20% as compared with the baseline, suggesting its therapeutic potential. Neprilysin (NEP), Insulin degrading enzyme (IDE), Plasmin, Endothelin converting enzyme (ECE) 1, Angiotensin-converting enzyme ; all these proteinases have ability to degrade Aβenzyme. NEP inhibitor injection and/or NEP knockout mice showed decreased Aβ degradation and cognitive activities, while NEP over expression showed improved spatial memory and decreased Aβ levels.

A tyrosine kinase inhibitor Imatinib, cause increase of NEP protein, mRNA levels, and activity. Valproic acid leads to Up-regulation of NEP expression in experimental rats. The ApoE activates microglia and/or astrocyte to degrade Aβ and Decrease brain amyloid plaque burden and improve behavior functions in AD transgenic mice. Bexarotene, a nuclear receptor modulator and ApoE activator, needs to b explored for AD prevention. The receptor for advanced glycation end products (RAGE) resides in the blood vessel wall cells and transport Aβ in the brain. Low-density lipoprotein receptor-related protein-1 (LRP-1) mediates transport of Aβ peptide out of brain. Thus inhibition of RAGE and/or activation of LRP-1 may be therapeutic target for AD. Passive immunotherapy in AD patients with repeated IV human immunoglobulin against Aβ peptide resulted in stopped cognitive decline and slight improvement in functional scores. Bapineuzumab decreased total and phosphorylated tau levels in CSF without affecting Aβ level. LY2062430 and AN1792A are on Phase I and II clinical trials. Metal (mainly Cu, Zn and Fe) metabolism is involved in APP processing and tau hyperphosphorylation the pathophysiological events in AD. Thus chelators of Zn/Cu have been shown to inhibit Aβ aggregation in vitro and in vivo.

Clioquinol, a metal-protein-attenuating compound in phase II clinical trial inhibits zinc and copper ions from binding to Aβ thus improved cognitive function. Other metal chelators including XH1, DP-109, PBT2 have shown to decrease CSF Aβ42 (not plasma) as compared to placebo, hence improve cognitive function. PBT2, second generation 8-OH quinoline derivative of clioquinol available orally is advancing as a disease-modifying candidate drug for Alzheimer's disease. Cholesterol-rich diet increase β-secretase processing of APP while cholesterol lowering resulted in decreased Aβ production. Treatment with lovastatin resulted in decreased plasma Aβ level. Clinical trial with atorvastatin provides clinical benefit in AD patients. Rasagiline a bifunctional molecule in phase II trial with MAO-B inhibition and Anticholinesterase inhibition activity Phase II trial.[15]

TAU BASED THERAPIES

Tau is a microtubule associated protein normally present in neurons. In AD hyperphosphorylation of tau occur which forms the paired helical filaments (PHF) and impairs axonal transport. Thus clinical trials are targeting mechanisms including tau phosphorylation, post translational modifications, microtubule stabilizers, tau aggregation inhibitors and anti-tau immunotherapy. A Nonsteroidal anti-inflammatory drug salasalate in frontotemporal dementia (FTD) mouse models inhibit acetyltransferase p-300- induced tau acetylation. In mild to moderate AD, Nilotinib a c-Abl tyrosine kinase inhibitor in phase II trial clean tau by inducing autophagy. A small molecule TPI-287 in phase I trial stabilizes microtubules in AD. TRx0237 (LMT-X) targets tau accumulation now in phase III trials in patients with AD. A phase II study involving Nicotinamide is currently ongoing in mild to moderate AD patients. It has shown to prevent phosphorylation of tau in mice. A phase II trial involving AADvac-1, a synthetic tau peptide spanning residues 294-305 is ongoing on patients with AD. A phase I clinical trial with ACI-35, a synthetic peptide spanning human tau sequence 393-408 is ongoing in patients with mild to moderate AD. Phase II and III studies with Intravenous immunoglobulin (IVIg) an anti-inflammatory and immunomodulator is going on in subjects with mild cognitive impairment and AD. Two studies are going on in patients of early AD involving ABBV-8E12 a humanized anti-tau monoclonal antibody. [16]Increasing the activation of molecular chaperones might prevent the misfolding of tau, which would then reduce the development of NFTs. Heat shock proteins have been shown to activate chaperones thus prevent misfolding and even promote tau binding with microtubules.[17]

SYMPTOMATIC TREATMENT

As the dementia progresses in AD behavioral and psychological symptoms of dementia (BPSD) increases which thereby increase the caregiver burden. According to a large observational study, BPSD may be grouped into four major symptom clusters with high prevalence: psychosis (38% of the patients, e.g. delusions), affective symptoms (59%, anxiety and depression), hyperactivity (64%, e.g. aggression, disinhibition) and apathy (65%). Serotonin reuptake inhibitors are considered as the most efficient antidepressants in patients with AD having co morbid depression[18]. Other antidepressants used are combined selective noradrenalin and serotonin inhibitors (SNRIs) and bupropion. Agitation and aggression in patients of AD dementia can be treated with antipsychotics

especially the atypical agents as they have milder parkinsonian effects. But use of antipsychotics is controversial as higher cerebrovascular morbidity and mortality have been found with its use. Moreover it not only worsens cognitive impairment but also associated with higher risk of hip fracture and pneumonia. Other agents used are benzodiazepines but they are associated with more rapid cognitive and functional decline especially in elderly population.[19]

The Serotonin 6 receptor subtype expressed mainly in cerebral cortex and hippocampus is responsible for cognitive impairment in Alzheimer disease. Thus receptor antagonists cause an increase in neurotransmission and thus used for symptomatic relief. A phase II double blind placebo controlled RCT with Idalopiridine; a serotonin receptor antagonist has shown significant improvement on ADAS Cog scale in patients with mild to moderate AD. Currently four trials in phase III are going on in 3000 patients who are already on a stable dose of 10mg/day of acetyl cholinesterase inhibitor with mild to moderate AD. Another serotonin6 receptor antagonist RVT-101 has shown reversal of induced as well as age related learning deficits in rats and currently in phase III. Repositioning or repurposing of drugs aims to identify new uses for compounds already known to be safe in animals and humans, thereby reducing the time spent on safety testing and speeding the development of new therapies. Trials are going on many drugs to prove the efficacy of drugs in AD which were previously used for other diseases. Exenatide and Liraglutide in vitro work has shown to influence neuronal function through a number of pathways mediated by GSK3β, caspase 3 and glutamate and now both of them are in phase II trials .Rodent models of AD have reported protection of synapse activity, improvement in neuronal function and properties at therapeutic dosage of Liraglutide. The activity of acetylcholine and inflammatory agents is thought to be regulated by Angiotensin II (Ang II) hence in vitro studies has shown effect of ARBs on cognition. Losartan have been shown to reduce inflammatory markers in mouse models of AD progressing to phase II study in AD patients.[20]

STEM CELL THERAPY

Mesenchymal stem cells (MSCs); the multipotent cells are nowadays clinically explored s a new therapeutic for treating a variety of immune-mediated diseases. A phase II trial is going on safety and efficiency of umbilical cord derived Mesenchymal stem cells (UC-MSC) in patients with Alzheimer disease.[21] The neural stem cells (NSCs) are shown to reverse memory impairment. These cells were transplanted into aged triple transgenic mice with aggressive Aβ load and were found to ameliorate loss in spatial learning and memory *without* altering Aβ and tau pathologies.[22]

CONCLUSION

The ultimate goal for Alzheimer's disease pharmacotherapy is not merely to ameliorate symptoms, but to alter the onset or progression of the disease. Currently there are four drugs - Donepezil, galantamine, Rivastigmine, and Memantine. The numerous complex and interrelated biochemical pathways underlying neurodegeneration in Alzheimer's disease can provide numerous potential targets for therapeutic intervention. Gradual elucidation of the exact mechanisms of neurodegeneration will result in increasingly focused drug development efforts.

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