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A Review Ofrecent Advances in Alzheimer's Disease Treatment

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ABSTRACT:A worldwide health concern, Alzheimer's disease (AD) has a complex pathophysiology with no known cure. Targeting the fundamental characteristics of AD, recent treatment developments present encouraging opportunities for disease modulation. Immunotherapy, gene therapy, anti-tau therapy, and anti-amyloid medicines are all improving the body's defences against harmful proteins and reducing neuroinflammation. These tactics give fresh hope for more potent and long-lasting AD treatments by redefining the paradigm from symptomatic management to focused disease-modifying techniques. There is new promise for longer-lasting and more effective treatments because to ongoing research combining various techniques.

KEYWORDS: Alzheimer's disease, Amyloid beta plaques, Therapeutic approaches

I. INTRODUCTION:

Alzheimer's disease is a neurological illness that gradually impairs cognitive and behavioural abilities. It starts slowly. Memory, comprehension, language, focus, logic, and judgement are some of these abilities. Although AD does not directly cause mortality, it significantly increases a person's susceptibility to other problems that may ultimately result in death. Late-onset AD (LOAD) is the term for AD that usually appears after the age of 65. About 5% of AD patients have early-onset AD (EOAD), which is less prevalent and manifests before the age of 65. A more aggressive course of the disease results from EOAD's frequently unusual symptoms and delayed diagnosis.[1]

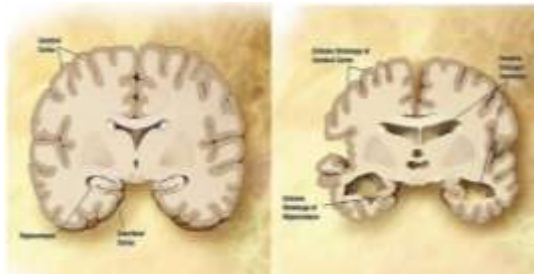

Fig 1. Structure of Normal and Alzheimer's Brain

ETIOLOGY

Slow and progressive neurodegeneration brought on by neuronal cell loss is a hallmark of AD. Both early-onset and late-onset AD have been linked to genetic variables. AD is a complex disorder with numerous established risk factors. Age is the most important component, and growing older is the main cause. Beginning at age 65, the frequency of AD about doubles for every five years of age gain. It is known that cardiovascular disorders (CVD) pose a serious risk for AD. They raise the chance of Alzheimer's disease (AD) as well as dementia brought on by strokes or vascular dementia. As a controllable risk factor for AD, CVD is becoming more widely acknowledged.[2]

SIGNS AND SYMPTOMS:

First signs and symptoms:

• Inability to focus on anything
• Inability to remember things that happened a few hours ago.
•Forgetfulness or absent-mindedness

Gettingsymptoms:

•Confusion
•Memory loss
• Difficulty carrying out daily duties

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•Difficulty reading or speaking clearly

Severesymptoms:
•Frequent depressive symptoms accompanied with apathy towards everyone and everything.
• Anxiety
• Aggression
•A lack of zeal and interest in day-to-day activities
•Total loss of cognitive ability.[3]

PATHOPHYSIOLOGY

Amyloid plaques and Tau tangles

One prevalent clinical feature of Alzheimer's disease (AD) is the presence of amyloid-beta plaques, which are a component of the amyloid precursor protein (APP). These plaques, which are mostly located in the hippocampus and cerebral cortex, hinder neuronal communication by causing neuroinflammation and disrupting synaptic function. Another connection between amyloid-beta plaques and the activation of immune cells, or microglia. AD is also associated with tau tangles, a protein that stabilises the microtubules of neurones and causes neuronal death.[4]

Neuroinflammation, Oxidative Stress, and Mitochondrial Dysfunction

A major contributing element to Alzheimer's disease (AD) is neuroinflammation, with astrocytes and microglia being essential components of the inflammatory response brought on by tau tangles and amyloid-beta plaques. Reactive oxygen species, inflammatory cytokines, and toxic compounds are released by chronically activated microglia, harming neurones and causing oxidative stress, brain barrier breakdown, and progressive neurone loss. While oxidative stress, a major factor in AD, is connected to neuronal dysfunction, this maladaptive neuroinflammation speeds up the neurodegenerative process. The health of neurones depends on mitochondria, but when they fail, neurodegeneration and cognitive declineare accelerated.[5]

Synaptic loss and Neuronal death

The pathogenic features of Alzheimer's disease (AD) include synapse loss and neuronal death. Amyloid-beta toxicity and tau illness can affect synaptic connections between neurones. Learning and memory are impacted by amyloid-beta plaques because they alter synaptic plasticity. Tau tangles interfere with the supply of proteins and nutrients to synapses by breaking apart microtubules. Neurones degenerate when synaptic loss rises, especially in crucial areas like the cortex and hippocampus. Cognitive decline and clinical symptoms such impaired executive function, memory loss, and disorientation result from this.[6]

II. ALZHEIMER'S DISEASE DRUG DEVELOPMENT

As of 2024, the U.S. Food and Drug Administration (FDA) has approved 12 medications to treat Alzheimer's disease (AD), while 127 medications are undergoing 164 clinical studies. With phase I studies comprising 25 medications and phase II trials involving 81 drugs, phase III trials are now complete. In 2023–2024, new medications such as lecanemab and donanemab were licensed. These medications, however, frequently have adverse effects and can only slow or stop the progression of AD. There is little clinical use, and the majority of medications are regularly tested for safety and efficacy. An estimated $6 billion is spent annually on AD medication development in the United States, according to the National Institutes of Health. Globally, more than $600 billion has been spent on AD research & development.[7]

Development of Amyloid beta targetingAD drugs

Aβ-targeting treatments have been shown in recent research to lower the burden of brain plaque and halt the course of Alzheimer's disease (AD). Reducing the formation of Aβ, boosting the clearance of Aβ or its aggregates, preventing or preventing Aβ aggregation, and lessening the harmful consequences of Aβ aggregates are some of these treatments. These treatments' advantages and disadvantages offer important insights for upcoming medication development.[8]

The FDA has approved three Aβ-targeting medications to treat Alzheimer's disease (AD). A human monoclonal antibody called acudanumab specifically targets aggregated Aβ. EMERGE and ENGAGE clinical studies assessed its safety and effectiveness in patients with early-stage AD. Despite conflicting results, the FDA granted expedited approval in 2021. In 2026, ENVISION, a post-approval confirmatory trial, is anticipated. Strict patient selection, titration to the maximum dose, and monitoring for amyloid-related imaging abnormalities were the recommendations of an expert panel in 2022. In patients with symptomatic ARIAs, treatment should be stopped or paused.[9]

In 2024, lecanemab, a humanised IgG1 monoclonal antibody, received approval due to its

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moderate selectivity for fibrillar amyloid and strong selectivity for soluble Aβ aggregates. In individuals with moderate cognitive impairment or dementia, the CLARITY AD trial demonstrated significant decreases in amyloid plaque load, delaying cognitive decline by 27% and 37%, respectively. By specifically targeting the insoluble, modified N-terminal truncated forms of Aβ present in amyloid plaques, donanemab, a monoclonal antibody intended to remove cerebral amyloid plaques, facilitates the elimination of plaques by microglia-mediated phagocytosis.[10]

Lecanemab and aducanumab have both shown promising outcomes in clinical trials; nevertheless, they have drawbacks, such as side effects that are comparable to those of aducanumab. Side effects from infusions are frequent; 40% of individuals need paracetamol or antihistamines. Amyloid-related image abnormalities-oedema or effusion (ARIA-E) or ARIA-H are 17% more common in lecanemab-treated participants, particularly in those who had the homozygous ApoE4 genotype. Professors Whitehouse and Saini contend that aducanumab ought to be discontinued because of its ineffectiveness, contradictory evidence, and adverse effects. The FDA Advisory Committee came to the conclusion that the medication was ineffective. When creating anti-Aβ medications to treat AD, population differences should be taken into account. Although some patients experience a slowdown in their cognitive and functional decline, the effectiveness of these medications is still debatable.[11]

Development of Tau targeted AD drugs

The development of tau-targeted therapies, especially for the treatment of Alzheimer's disease (AD), depends heavily on tau biomarkers. The initial generation of tau-targeted therapies concentrated on either directly preventing tau aggregation or reversing it, such as through hyperphosphorylation. By eliminating or preventing the aggregation of tau aggregates, current research involves tau immunotherapy and techniques to target tau production, which halt the progression of the disease. While methods aimed at tau production concentrate on lowering tau production or acting before aggregate formation, immunotherapy employs antibodies to directly target tau in order to lessen the harm that tau aggregation does to the nervous system. The majority of tau immunotherapies focus on MTBR or N-terminal domains.[12]

The safety of leuco-methylthioninium (LMT) and zagotenemab's inability to decrease the development of the illness are two limitations of clinical research on tau-targeted medications for AD. There is no indication of pharmacological activity or disease change in imaging biomarkers or plasma NfL findings. Uncertainty surrounds the pharmacological mechanism of tau, and research on the effectiveness of the majority of medications in individuals with moderate tau load is lacking. In current and upcoming AD trials, the binding characteristics of various anti-tau compounds may prove beneficial. [13]

Development of drugs targeting the cholinergic system in AD patients

Drugs that target the cholinergic system, including galantamine, donepezil, rivastigmine, and tacrine, have been developed to treat Alzheimer's disease (AD). These medications can help AD patients with their cognitive symptoms by raising ACh levels in the synaptic gap. Cholinergic lesions are predominantly presynaptic and manifest early in the asymptomatic or prodromal phase of the disease. In 1993, the FDA authorised tacrine, a reversible anticholinesterase inhibitor. High-dose tacrine improved outcomes for AD patients, according to a clinical trial including 663 participants. 663 people in all received varying dosages of tacrine during the trial. The findings demonstrated that medications that target the cholinergic system can aid people with AD with their cognitive symptoms and neuropathological diagnosis.[14]

In 1995, the FDA approved a Chinese herb monomer called huperzine A because it selectively inhibits acetylcholinesterase, improving its function. It improves learning and memory in Alzheimer's disease (AD) patients by stimulating cholinergic neurones and increasing acetylcholine production. Its safety and effectiveness were assessed in a clinical experiment with 202 AD patients. The most potent inhibitor of AChE in brain tissue is donepezil, a reversible central AChE inhibitor that was authorised in 1996. The effectiveness and safety of various donepezil dosages in AD patients have also been examined in clinical trials.[15]

Rivastigmine, a carbamate-selective acetylcholinesterase inhibitor, was approved by the FDA in 2000 to improve cognitive efficiency in Alzheimer's patients. Clinical studies have shown that rivastigmine patches are better tolerated than capsules. Galantamine, originally isolated from snowdrop and daffodil bulbs, was approved in

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2005 and showed significant improvement in core symptoms of Alzheimer's disease compared to placebo. Both drugs have shown efficacy and tolerability in treating Alzheimer's disease. Both drugs have been used in clinical trials to assess cognitive function and tolerability.[16]

Development of drugs targeting Neuroinflammation

According to recent research, inflammation is a major factor in the onset of Alzheimer's disease (AD). Based on a clinical investigation involving individuals with Dementia of Alzheimer Type (DAT) dementia, the FDA authorised idebenone in 2000. According to thestudy, idebenoneconsiderably raised the ADAS-Total and ADAS-Cog scores, the primary efficacy measures. There have been reports of the medication's safety and effectiveness, and throughout the first year of treatment, it shown long-lasting effectiveness. In the second year, additional improvements were noted, indicating that idebenone slowed the disease's course. This implies that idebenone has a positive therapeutic impact on the advancement of AD.[17]

For people with mild to moderate Alzheimer's disease (AD), the oral tyrosine kinase inhibitor mastibinib has been investigated as an adjuvant treatment. It may help people with mild to moderate AD by suppressing mast cell and microglial/macrophage activity. A glucagon-like peptide-1 receptor agonist called semaglutide is used to treat type 2 diabetes and obesity. Its safety profile is well-established, and the most common side effect is gastrointestinal disruption. GLP-1RAs maintain synaptic function, improve glial cell homeostasis, control adaptive immunological responses, alter biological pathways pertinent to AD pathology, and have neuroprotective effects. Neuroinflammatory indicators in early-symptomatic AD were attenuated, and the incidence of dementia was significantly reduced, according to a Phase III experiment.[18]

In patients with Alzheimer's disease (AD), chronic local inflammatory responses in pathologically sensitive brain regions are a well-known occurrence. Anti-inflammatory medication may help postpone the beginning of AD or reduce its course. Targeting neuroinflammation to treat AD has drawbacks and unknowns, though. More research is still needed to determine how long anti-inflammatory treatments will last because AD-related inflammation is weak but chronic, causing serious harm over many years.[19]

III. ADVANCES IN ALZHEIMER'S DISEASE TREATMENT

1. Anti-amyloid therapy

The APP is the source of amyloid plaques, which are made up of A peptides and build up in neurotoxicity. One of the treatment objectives for Alzheimer's disease is to decrease A buildup.[20]

a) Secretase Inhibitors:

The catalytic activities of secretase, the rate-limiting step in the synthesis of A, are the focus of secretase inhibitors. In patients with mild to moderate AD and mild cognitive impairment (MCI), a number of BACE1 inhibitors have advanced to phase III clinical trials but have failed because of ineffectiveness or worsened cognitive function. With some being stopped in double-blind randomised controlled studies and cognitive decline seen in people with MCI and mild to moderate AD, the function of secretase inhibitors is still up for question.[21]

b) Aβ aggregation Inhibitors:

Because of their tiny size, absence of particular pockets or grooves, and poor permeability through the blood-brain barrier, natural substances having aggregation inhibitory effects have often been opposed for clinical use. Targeting brain chaperones, such metals, that interfere with the interaction between A peptides and metals, is one tactic. Copper and zinc ions are chelated by metal protein attenuating compounds (MPACs), which also prevent A aggregation. For example, in patients with mild to moderate Alzheimer's disease (MCI), clioquinol (PBT1), a hydroxyquinoline ionophore, did not significantly enhance clinical global impression or cognition. Although it was proven to be safe and well-tolerated in mild AD, second-generation clioquinol (PBT2) had no discernible impact on function or cognition.

Potential molecules for the treatment of Alzheimer's disease (AD) have been identified by advanced biophysical and structural biology experimental techniques. Certain substances, such tanshinone and uncarinic acid C, enhance the inhibitory effects of A aggregation. Others interact with A toxicity determinants, such as resveratrol and EGCG.[22]

2. Anti- Tau therapy

Microtubules are stabilised in axons and dendrites by the tau protein. It experiences post-translational changes, especially

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hyperphosphorylation, which results in the formation of neurofibrillary tangles (NFTs), which trigger inflammatory reactions and neurotoxicity. The degree of cognitive impairment in Alzheimer's disease (AD) is correlated with tau pathology. Phosphatase modifiers, kinase inhibitors, and tau immunotherapy are examples of anti-tau therapeutic techniques.[23]

a) Kinase Inhibitors:

Kinase inhibitors, which are associated with the protein kinases CDK5 and GSK3, limit the hyperphosphorylation of tau and reduce post-translational changes. Roscovitine and flavopiridol are two examples of selective CDK5 inhibitors that have been used in cancer treatment. Roscovitine decreased memory loss and stopped tau phosphorylation in animal models of Alzheimer's disease (AD). None of these medications have advanced to clinical trials in AD, though. Lithium and tideglusib, two varieties of GSK3 inhibitors, have been studied in AD. While lithium, a mood stabiliser, had a moderate effect size in slowing the trajectory of cognitive deterioration in AD patients, tideglusib did not demonstrate any clinical benefit in phase II trials. To ascertain its efficacy in treating AD, more research is required.[24]

b) Tau Aggregation Inhibitors:

One synthetic phenothiazine dye that inhibits tau aggregation early on is methylene blue (MB). It interferes with polymerisation and prevents tau connections. While MB derivative LMTX failed, a phase II double-blind RCT shown cognitive improvements in mild to moderate AD. MB has an ambiguous effect in AD treatment since it prevents the creation of tau fibrils but speeds up the production of hazardous tau oligomers.

By reducing tau sheet formation and breaking down tau oligomers, the dietary ingredient and colouring curcumin prevents tau from aggregating. However, because of its low bioavailability, prior research on Alzheimer's disease patients found no change in cognitive function following a 6-month course of treatment. According to a new meta-analysis, curcumin therapy impairs AD patients' cognitive function.[25]

3. Anti-Neuroinflammatory therapy

The severity of AD is correlated with neuroinflammation, which also plays a role in the disease's progression.[26] Insulin resistance control, microbiota therapy, astrocyte modulators, and microglia modulators are examples of anti-neuroinflammatory techniques.

a) Astrocyte Modulators:

The Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3), calcineurin/NFAT, nuclear factor-kB/nod-like receptor family pyrin domain containing 3 (NFB/NLRP3), mitogen-activated protein kinase (MAPK), and P2Y1 purinoreceptor (P2Y1R) are among the signalling pathways involved in the astrocyte reaction in Alzheimer's disease (AD). In AD animal models, Stattic, a specific STAT3 inhibitor, has been demonstrated to improve memory and learning deficits. In APP/PS1 mice, FK506 (Tacrolimus) alleviated the cognitive loss by blocking the calcineurin/NFAT pathway. Animal studies of AD have examined P38 MAPK inhibitors, including SB202190 and PD169316.[27]

b) Microbiome Therapy:

Through the synthesis of neurotransmitters and neuromodulators, the gut microbiota plays a critical role in gut-brain communication and brain function. An excess of LPS is produced as a result of gut microbiota dysbiosis, which increases blood-brain barrier permeability. A marine-derivedoligosaccharide called sodium oligomannate destabilises A aggregates, controls neuroinflammation, and inhibits dysbiosis of the gut microbiota. Patients with mild to severe Alzheimer's disease (AD) benefited cognitively, according to phase III double-blind RCTs. In November 2019, China approved sodium oligomannate.[28]

4. Gene Therapy

The goal of gene therapy treatments is to fix damaged proteins, genes, or DNA at the root cause of illnesses like Alzheimer's. Recent advancements in recombinant adeno-associated virus (rAAV)-associated gene therapy techniques hold promise for treating these illnesses in people. Tuszynski et al. (2015) investigated the potential of a nervous system growth factor (NGF) to degrade neurones in Alzheimer's disease (AD). The findings demonstrated activation of functional indicators, cell hypertrophy, and favourable neuronal responses. Another study shown that introducing the gene PGC1-alpha into the brain cells of mice prevented the development of Alzheimer's disease, leading to better memory, no brain cell loss, and less amyloid plaques.Through intracerebral gene transfer, the study seeks to lower amyloid-β production in Alzheimer's disease patients. The

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viability of stereotactic gene transfer under sham surgery management in AD patients was shown in a randomised clinical experiment. Delivery of AAV2-NGF (adeno-associated viral vector, serotype 2) was possible but did not provide any clinical results. The exact gene targeting in the study needs to be confirmed. Using a genetic snipping approach to change the APOE4 gene into APOE3, researchers at the Massachusetts Institute of Technology found a cure for Alzheimer's disease in June 2018. The solution to this problem may lie in gene editing.[29]

5. Immunotherapy for AD

Aβ immunotherapy uses a number of processes, such as direct techniques, phagocytosis, and soluble equilibrium. Antibodies attach to amyloid seed in the early stages to stop its spread, neutralise and solubilise Aβ plaque, and promote microglia-associated phagocytosis. The peripheral sink mechanism and the direct approach are further mechanisms.

The main focus of immunotherapy for Alzheimer's disease is amyloid beta plaques. Numerous approaches, such as passive and active immunisation, are being researched. B-cells, T-cells, and microglia are stimulated by active immunisation with Aβ-42, whilst monoclonal antibodies (mAb) such as bapinezumab, solanezumab, gantenerumab, crenezumab, and ponezumab are being studied for passive immunisation. However, the majority of medications have serious adverse effects, like hemosiderosis, micro haemorrhage, and ARIA-E.

Aducanumab, SAR255952, BAN2401, and other engineered antibodies are now in the development stage. These antibodies target the N-terminus of Aβ3-6, large soluble Aβ protofibrils, and soluble protofibrillar and fibrillar Aβ species. Their binding activity at Fcγ regions is poor.[30]

IV. CONCLUSION

Instead of treating symptoms, recent developments in Alzheimer's disease treatment are concentrating on disease-modifying techniques. Anti-tau and anti-amyloid treatments have demonstrated encouraging outcomes in reducing cognitive deterioration. Immunotherapeutic strategies are being improved for increased efficacy and safety. Gene therapy is becoming more popular as a means of modifying important biochemical processes and fixing genetic mutations linked to AD. These developments offer a multifaceted strategy for managing AD and raise the prospect of more potent treatments. These therapies are opening the door for individualised and possibly curative treatments, notwithstanding issues with patient stratification and long-term safety.

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