Review Article

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Recent Advances in Treatment of Alzheimer's Disease

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Abstract

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder that is the leading cause of dementia across the globe, especially in the elderly. It is characterized by progressive decline in cognitive function and memory, accompanied by behavioral changes, which leads to neuronal death and eventually complete dementia and death. However, it is encouraging to note that several new treatments for AD are on the horizon. This review highlights some of these new therapeutic strategies, including gene therapy, immunotherapy, peptidomimetics, and metal chelators. It is anticipated that these therapies will provide hope for the millions of patients across the globe suffering from this debilitating disease.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and is the major cause of dementia worldwide. It is one of the principal healthcare challenges and a major puzzle in medical science. Currently, there are approximately 50 million people living with AD globally [1].

Alzheimer's disease initially presents clinically with an insidious impairment of cognitive function, and within a decade, results in debilitation, often encompassing severe memory loss, confusion, behavior and personality changes, speech dysfunction, an inability to live independently, and ultimately a near-vegetative state [2].

As per the World Health Organization (WHO) update on the epidemiology of AD in 2013, the number of people suffering from dementia worldwide is likely to triple by 2050, which was approximately 35.6 million in 2010 [3]. Most AD cases have an onset after 65 years of age, accounting for 5-10% of this age group, and this number increases to 50% in people older than 85 years [4]. The prevalence of AD in men is lower than that for women by 19-29%. China, USA, India, Japan, Germany, Russia, France, and Brazil were the eight countries in descending order of incidence of dementia in 2010. Alzheimer's patients usually succumb within 5-12 years of disease onset [5].

The main neuropathological hallmarks of AD include two intertwining molecular cascades, i.e., the extracellular accumulation of amyloid-β peptide (Aβ), resulting in deposition of β-amyloid plaques in brain parenchyma and the formation of intraneuronal aggregates of hyperphosphorylated tau protein, termed as neurofibrillary tangles [6]. These proteins are the precursors for the loss of connections between nerve cells, eventually leading to nerve cell death. The β-amyloid plaques, comprising of tau amyloid fibrils are associated with memory impairment and other cognitive problems (Figure 1) [7].

There are various risk factors for developing AD, including age, obesity, diabetes, brain inflammation, infections, and genetic predisposition.

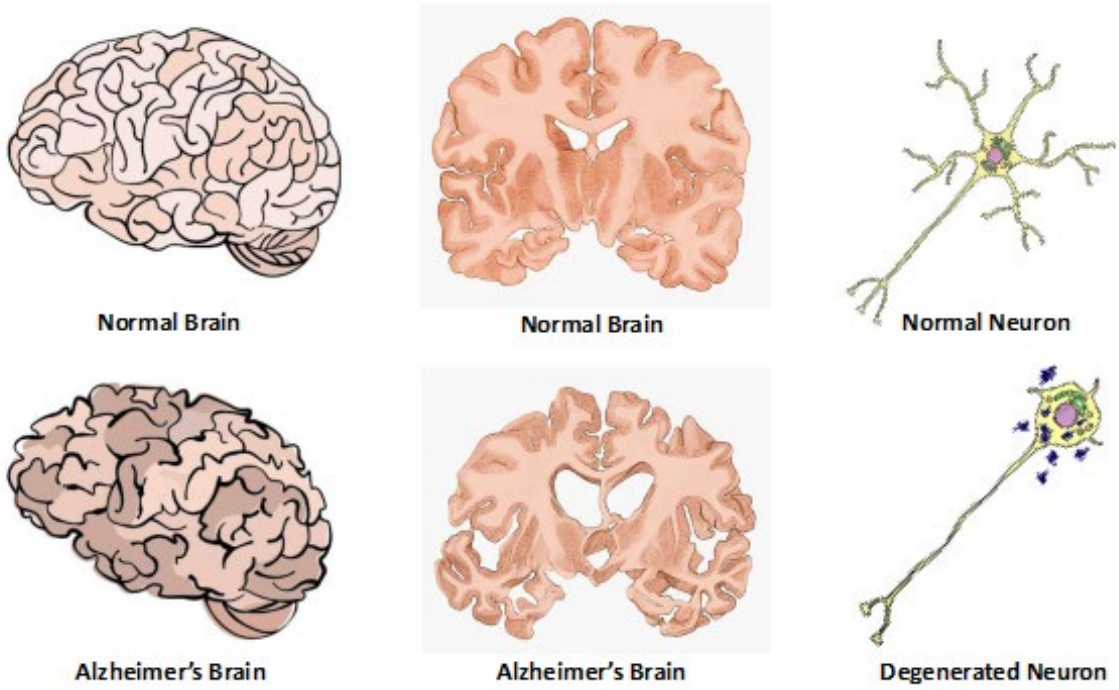

Figure 1: Pathological Changes in the Brain and Neurons of Alzheimer's Patients Compared to Healthy Individuals

1.1. Treatments Under Development for Alzheimer's Disease

There are various treatment modalities for AD that are being developed. Some of these approaches are highlighted below (Figure 2).

Figure 2: Latest Treatment Strategies for Alzheimer's Disease

1.2. Gene Therapy

Gene therapy holds promise for treating a wide range of diseases. This strategy is used to replace a faulty gene or add a new gene or repair the faulty gene, thereby allowing the cells to recover and improve the condition. Recent developments in gene therapy associated approaches employing recombinant adeno-associated viruses (rAAVs) allow treatment of diseases like AD. Nerve growth factor (NGF)-based gene therapy has shown positive neuronal responses in AD patients that lasted for a decade [8]. Gene therapy studies in mice with the PGC-1α (peroxisome proliferator-activated receptor-γ coactivator-1α) gene, showed improvement in memory, reduction of hippocampal cell loss, and decrease in amyloid plaques, four months following gene delivery into mice brains using a recombinant viral vector [9]. A randomized clinical trial was conducted, employing stereotactic gene delivery into the brain of AD patients. The trial used an adeno-associated viral vector containing the NGF transgene. This strategy was found to be feasible and well-tolerated, but didn't show any clinical benefits [10]. The newly developed CRISPR-Cas9 gene editing tool is one of the most powerful technologies for correcting undesired genetic mutations and is likely to have important applications in the treatment of AD [11].

1.3. Immunotherapy

There are two types of immunotherapies – active and passive (Table 1 and 2). Research on both approaches is in progress to develop treatments for AD that specifically target Aβ. Active immunization with Aβ is mediated by B-cells, T-cells, and microglia. In case of monoclonal antibodies (mAb) like bapineuzumab, solanezumab, gantenerumab, crenezumab, and ponezumab, among others, passive immunization is used.

Vaccine	Mechanism
ACI-24	Generates antibodies against Aβ without activating inflammatory cells
ACI-35	Liposome based vaccine that generates antibodies against phosphorylated tau
ABvac40	Targets C-terminus of Aβ40
AADvac-1	Peptide vaccine that generates antibodies against tau
CAD106	Viral vaccine that targets Aβ without activating T-cells
LuAF20513	Generates anti-Aβ antibodies without microglial activation
DNA vaccine	Translation of Aβ DNA leads to generation of antibodies

Table 1: Active Immunotherapy

Drug	Mechanism
Aducanumab	mAb against Aβ
Crenezumab	Humanized mAb that targets polymorphic form of Aβ
Gantenerumab	Binds to Aβ and induces phagocytosis by activating microglia
BAN2401	Preferentially binds to soluble protofibrils of Aβ
Bapineuzumab	Humanized murine mAb that targets N-terminal region of Aβ
Solanezumab	Targets monomeric and non-fibrillary form of Aβ
BIIB092	Targets N-terminal fragment of tau
C2N 8E12	Targets extracellular tau aggregates

Table 2: Passive Immunotherapy

Several hypotheses exist regarding Aβ immunotherapy, such as soluble equilibrium mechanism, phagocytosis mechanism, peripheral sink mechanism, and direct method, among others.

Various engineered antibodies or second-generation antibodies are currently under development. These have low binding affinity to the Fcγ regions, which were responsible for the side effects exhibited by the first generation mAbs.

Recent approval of aducanumab for the treatment of AD demonstrates how close passive immunotherapy is to being successful.

Targets beyond Aβ, such as tau and some additional microglia-based immunotherapies targeting various immunological molecules such as TREM2 (triggering receptor expressed on myeloid cells-2), CD38 and Toll-like receptors (TLRs) are also under investigation.

1.4. Immunotherapy Based on Tau Protein and Microglia

Tau is a brain-specific, axon-enriched, microtubule-associated protein that causes neurodegeneration, which is a hallmark of AD. Tau protein appears to be better correlated with the severity of cognitive decline than Aβ in AD, indicating the therapeutic approach targeting tau should be promising. Currently, most anti-tau agents in immunotherapies include active vaccines like AADvac1 and ACI-35 and passive immunotherapeutic antibodies such as semorinemab, gosuranemab, and BIIB076, which have emerged in recent years. They all have significant therapeutic effects in animal models of AD [12].

A growing number of genome-wide association studies (GWAS) have demonstrated that many AD risk genes, such as TREM2, are highly expressed on microglia, indicating that these molecules can be promising targets for antibodies to modulate microglial function and the neuroimmune system in the brain [13].

Although sodium oligomannate is not regarded as a traditional immunotherapeutic drug, it reduces microglial activation and neuroinfammation, and consequently slows cognitive decline by regulating gut microbiota and the gut-brain axis [14] and has been approved by China's National Medical Products Administration (NMPA) for treating mild to moderate AD [15].

1.5. Peptidomimetics

Protein misfolding and aggregation are common features of neurodegenerative diseases like AD, which occurs due to characteristic protein-protein interactions. A peptidomimetic is a small peptide designed to mimic the structural elements and functionality of natural peptides or proteins in 3D space and which retains the ability to interact with biological targets to exhibit equivalent or superior biological effects. These peptides prevent protein-protein interactions to inhibit aggregation.

Amyloid-β peptides are proteolytic fragments of the transmembrane amyloid precursor protein and the main component of senile plaques found in the brain of AD patients. These are the molecular targets for AD therapeutic intervention. Peptidomimetics against Aβ aggregates have been designed to target the central hydrophobic core or the C-terminus. Various potential AD therapeutics include inhibitors of β-secretase, γ-secretase, and Aβ aggregation, and anti-amyloid agents [16].

Peptidomimetics has also been applied in the context of tau aggregation. The effect of Aβ derived peptidomimetics on tau aggregation was studied. It was found that these peptides decreased thioflavin S (ThS) fluorescence in heparin-induced tau

aggregation. Transmission Electron Microscopy (TEM) images suggested the inhibition of tau assembly into fibrillar aggregates [17].

1.6. Metal Chelators

Metal ions (Cu, Zn, and Fe), as well as Ca are critical for the pathogenesis of several neurodegenerative disorders, including AD. Metal chelators are inorganic or organic compounds that bind to metal ions and form non-toxic complexes having a ringed structure, technically termed as 'chelates'. These are capable of disrupting metal-protein interactions and may serve as therapeutic agents for the treatment of neurodegenerative diseases [18].

Some studies have reported the use of metal chelators for modulating metal induced neurodegeneration and it has been demonstrated that Cu, Zn, and Fe chelators efficiently inhibit the aggregation of Aβ fibrils [19].

In the brain of AD patients, Cu, Zn, and Fe are the major metal targets for chelation. Some common chelator drugs that have shown favorable results include deferoxamine (DFO), bathophenanthroline, bathocuproine (BC), trientine, penicillamine, bis (thiosemicarbazone), and tetrathiomolybdate (TTM) [20].

Deferoxamine and its derivatives, which have comparatively more affinity for Fe ions than other chelators, are used to treat memory impairment and prevent Fe-induced neurotoxicity and reactive oxygen species (ROS) generation. There are also other chelator analogues that exhibit differential affinity for metallic ions, such as Cu [21]. One such Cu chelating agent is TTM, which can lower both the level of Aβ and Aβ plaques formed in the brain [22]. Besides these, there are other metal chelation approaches that could be used as potential therapeutic agents for AD. These include multifunctional compounds (MC), such as metal protein attenuating compounds (MPACs) [23, 24] and Rhodamine-B-based metal chelators like Rh-BT. MPACs help to solubilize Aβ protein and prevent oxidative stress-mediated damage to Aβ [25]. Rh-BT exhibits blood-brain-barrier (BBB) permeability and can effectively capture redox metal ions from the Aβ-Cu2+ complex, thereby decreasing metal-induced ROS production. It is also capable of inhibiting Aβ self-assembly into toxic oligomeric and fibrillar aggregates [26].

2. Conclusion

From the foregoing discussion, it is clearly evident that AD is a serious problem, affecting millions of people worldwide. Though great strides have been made in elucidating the pathophysiology of the disease, the complete picture is yet to emerge. With reference to development of therapies against the disease, research is in full swing and it is beyond any doubt that scientists are making sincere efforts to develop a treatment that would ideally be curative. However, for the moment, a definitive treatment still eludes us. Having said this, the therapeutic strategies that have been highlighted in this review are indeed very promising. All of these are new, innovative, and novel strategies. They hold the potential to be a game changer and bring about a paradigm shift in the way AD patients are treated. Hence, these are exciting times for doing research in this area of scientific endeavor.

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