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MINIREVIEWS

New treatment modalities in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is still a major public health challenge without an effective treatment to prevent or stop it. Routinely used acetylcholinesterase inhibitors and memantine seem to slow disease progression only to a limited extend. Therefore, many investigations on new drugs and other treatment modalities are ongoing in close association with increasing knowledge of the pathophysiology of the disease. Here, we review the studies about the new treatment modalities in AD with a classification based on their main targets, specifically pathologic structures of the disease, amyloid and tau, neural network dysfunction with special interest to the regulation of gamma oscillations, and attempts for the restoration of neural tissue via regenerative medicine. Additionally, we describe the evolving modalities related to gut microbiota, modulation, microglial function, and glucose metabolism.

Key words: Alzheimer's disease treatment; Anti-amyloid; Anti-tau; Gamma oscillations; Stem cell therapy

Core tip: This review discusses various new treatment modalities in Alzheimer's disease (AD) based on the classification of their mechanism of action. New anti-amyloid, anti-tau, and treatments targeting network dysfunction with particular attention to deep brain stimulation to modulate gamma oscillations in the brain are evaluated. Moreover exciting developments in stem cell therapy especially combined with tissue engineering techniques are presented. Lastly some other modalities including microglial function modulators, gut microbiome transplantation, modulation of vagus nerve and metabolic arrangements are mentioned. It seems that new treatments in AD will involve each of them individually or in combination.

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INTRODUCTION

Alzheimer's disease (AD) is a major public health challenge in the 21st century. For this reason, near to 500 clinical trials have been conducted and huge amounts of money have been spent in an effort to handle the disease[1]. At present, cholinesterase inhibitors donepezil, rivastigmine, and galantamine and, memantine, which acts as a N-methyl D-aspartate receptor antagonist and also as a dopamine antagonist, are approved as symptomatic treatments for use in AD[2,3]. Other alternative treatments and measures include nutraceutical huperzine A, correction of vitamin D deficiency, use of non-steroidal anti-inflammatory drugs, omega 3 fatty acid supplements, management of cardiovascular risk factors, and aerobic physical exercise[4-8]. The benefits of these options are limited to slowing the disease, not matching the expectation of stopping it.

With advances in molecular biology and pharmacology, some new treatment modalities related to the pathognomonic pathological features of the disease have come onto the scene. Additionally, new therapeutic neurophysiological interventions have aimed to resolve the neural network dysfunction that emerge through progression of the disease, and trials of stem cell therapy have been initiated. Early therapeutic intervention is an important factor for the success of treatment. Moreover, some environmental regulations can be considered as measures of prevention, especially in persons who are at high risk of developing AD.

Here, we review investigations on the new treatment modalities in AD with a classification based on their main targets, specifically pathologic structures of the disease (*i.e.*, amyloid and tau), neural network dysfunction with special attention to the regulation of gamma oscillations and attempts for the restoration of neural tissue *via* regenerative medicine. Additionally, we describe the evolving modalities related to gut microbiota, modulation, microglial function, and glucose metabolism.

ANTI-AMYLOID

Amyloid plaques are the earliest manifestation of AD, and can be detected 20 years prior to the onset of symptoms[9]. The most direct action in anti-Amyloid treatment is to reduce Amyloid-β (Aβ) production from its precursor, Amyloid precursor protein (APP), by targeting β and γ-secretases, but some safety problems exist for these drugs. For γ-secretase inhibitors, unwanted side effects are unavoidable due to its physiological substrates, which are essential in normal biological processes, such as the Notch signaling protein[10]. β-Amyloid secretase inhibitors (β-site APP cleaving enzyme 1: BACE1) have some challenges such as the large catalytic pocket and adverse side effects including blindness[11]. Additionally, there are some handicaps with the use of these drugs, because the majority of AD patients do not have over-produced APP and some Aβ isoforms can increase neurotransmitter release at hippocampal synapses by some regulatory mechanisms [12].

Though early investigations of BACE1 inhibitors failed to show meaningful results in human subjects, a recent study declared that the novel medication verubecestat caused a decrease in Aβ levels at a level of more than 40 fold in animals and showed good safety profile in early human trials[13] (Table 1).

Another approach for decreasing Aβ plaque deposition is immunotherapy. Although active Aβ-immunotherapeutic agents showed some beneficial clinical effects, the studies were suspended due to serious side effects such as meningoencephalitis[14-16]. Monoclonal antibodies initially developed as passive immunotherapy agents removed plaques from the brains of patients, but did not improve cognitive scores in patients with mild to moderate disease[17-25]. These results have led investigators to believe that these agents may be beneficial solely in the early phases of mild cognitive impairment. Solanezumab did not yield beneficial clinical effects in patients with few symptoms, despite some improvements in amyloid PET imaging and in assessments of Mini Mental State Examination[21,22,26-30]. Another agent named aducanumab is currently under investigation (EARLY study) for its clinical effects in elderly persons with positive biomarkers or family history of AD, and has promising initial results[21,22,26-30].

To overcome the failures with monoclonal antibodies, multiple functional subregi-

Table 1 Potential treatments related to BACE1 and p-tau undergoing clinical trials

Target	Drug	Study phase	Expected completion date	Results
BACE1	Lanabecestat	2	September 2019	
	JNJ-54861911	2	October 2022	
	Elenbecestat	3	December 2020	
	Verubecestat	3	March 2021	
	LY450139	3	Completed April 2011	Not effective
P-tau	IONIS-MAPTRx	1, 2	February 2020	
	JNJ-63733657	1	February 2019	
	RO7105705	2	September 2022	
	ABBV-8E12	2	June 2021	
	AADvac 1	2	June 2019	
	BIIB-092	2	September 2020	
	BIIB-080	1	February 2020	
	TPI-287	1	Completed May 2017	
	TRx0237	3	February 2019	
	LY3303560	1	June 2019	
	MTAU9937A	2	(-) Continuing	
	E2814	1	(-) Continuing	

BACE1: β-site amyloid precursor protein cleaving enzyme 1; p-tau: Hyperphosphorylated tau peptide.

ons of Aβ may be targeted[31]. Moreover, combination therapy with a monoclonal antibody and BACE1 inhibitor may be more promising, because it has been shown to reduce the amount of amyloid plaques in mice significantly[32]. Despite many problems, immunotherapy is still a promising approach to modify the extend of neuro-degeneration in AD[33].

ANTI-TAU

Since the anti-amyloid treatment measures have not been as successful as expected so far, some other targets are starting to being investigated. Tau-targeted trials are the major new interest for this aim, since biomarker studies propose that tau pathology is closely correlated to the clinical follow up of AD[34]. Initially, inhibitors of kinases and tau aggregation or stabilizators of microtubules were tried as potential anti-tau therapies. However, most of these approaches have failed because of their toxicity and/or lack of efficacy. Recently, most of the anti-tau clinical investigations are based on immunotherapeutic approaches. There are 8 ongoing clinical trials, (in Phase I, Phase II) and several preclinical studies on tau immunotherapies. TRx0237 as a tau aggregation blocker failed to yield beneficial treatment effects in a phase III trial[35]. Intravenous immunoglobulin, the passive immunotherapy among Phase III clinical trials, did not fulfill primary end points in mild to moderate AD[36]. AADvac1 as a tau vaccine showed good results in terms of both safety and immunological response in Alzheimer patients. Further studies are needed to prove its clinical efficacy[37] (Table 1).

Goldstein *et al*[38] reported that cholesterol esters (CE), the storage form of excess cholesterol within cells, regulate tau activity. Moreover, they found that the anti-HIV drug efavirenz decreased CE by activating the neuronal enzyme "CYP46A1" and thereby reduced phosphorylated tau within neurons of patients with AD. Furthermore, they observed that CE promotes formation of tau even in the absence of Aβ, indicating that simply removing Aβ from the brain, which was the target of many candidate drugs for AD treatment, would not be adequate to halt the disease. They thought that the CYP46A1-CE-tau axis was a target and a potential mechanism against which new drugs could be developed in the treatment of early AD. The researchers also confirmed previous reports declaring that reducing CE prevented amyloid formation additionally. They stated that CE were upstream of both Aβ and tau, presenting a way to prevent abnormal deposition of these proteins.

Key opinion leaders believe that the research field of tau therapies is still premature and trials may face the similar difficulties as in amyloid therapies[1]. However, if these trials become successful, they may cause enrichment in the alternative choices

including combination therapies against accumulation of pathologic amyloid and tau proteins, in the early stages of the disease.

TARGETING NEURAL NETWORK DYSFUNCTION

In recent years, it has been discovered that alterations at the genetic and cellular levels initiate neural network dysfunction which causes further deterioriation in cognition. Additionally, a novel hypothesis has been proposed, stating that AD patients are able to encode memories but unable to retrieve them[39]. Therefore, in addition to treatments targeting the pathological structures, strategies restoring neural network connectivity may be directly useful in reversing memory loss[40-45]. These therapeutic drugs and interventions also have positive feedback effects on molecular processes to re-establish cellular health[46].

Deep brain stimulation techniques used in Phase 1 studies to directly target the activity of brain networks ended with positive results[47,48]. Stimulation of the fornix in animal models changed protein expression and in turn restored cellular health and network function[49]. Likewise, increased histone acetylation using inhibitors of histone deacetylases in a mouse model caused the sprouting of dendrites and increased number of synapses, thereby inducing repair of neural networks and leading to recovery of learning behaviour and access to long-term memories[50]. Excitation of hippocampal engram cells using optogenetic techniques in a transgenic mouse model of early AD increased the number of dendritic cells and recovered learning and memory[39]. Arrangement of gamma oscillations in the hippocampus is also a new technique that has been shown to have positive effects on cognitive activity by restoring interneuron activity and by some non-neuronal effects[42].

Gamma oscillations are rthymic fluctuations of brain waves in local field potentials with a wide range of high frequencies (approximately 25-100 Hz) and are associated with inter-neuronal communication in virtually all brain networks. These oscillations may actually be two functionally distinct rhythms, slow (approximately 25-50 Hz) and fast (approximately 55-100 Hz) gamma[51]. Although slow and fast gamma waves are found to be generated locally, gamma oscillators with similar frequencies in various brain regions can be synchronized through anatomical connections[51]. There is growing evidence that gamma rhythms are important for hippocampal memory processing, as fast gamma stimulates new memory encoding by conveying current sensory information to the hippocampus [52,53] and slow gamma plays a role in memory retrieval by facilitating hippocampal CA3 inputs to CA1[51,52,54,55]. Sharp wave-ripples (SWRs)[54] are also important in memory retrieval, because slow gamma power and harmony between CA3 and CA1 increases during them[56,57] .

A decrease in SWR-associated slow gamma was demonstrated in AD mouse models. The rescue of slow gamma rhythms resulted in alleviation of deficits in learning-memory and mitigation of AD pathology by the modulation of gamma oscillations[40-43]. Hippocampal fast-spiking parvalbumin-positive interneurons were excited optogenetically by using a non-invasive 40 Hz photic stimulator. This technique also decreased Aβ production and stimulated its attenuation by increasing microglial engulfment[42].

RESTORATION OF NEURAL TISSUE *VIA* REGENERATIVE MEDICINE

Elimination or blocking of amyloid or hyperphosphorylated tau protein cannot restore or replace the degenerated neurons in AD. Stem cell therapy seems to be a convenient candidate for repopulation and regeneration of degenerating neuronal networks in the disease. The designs of stem cell therapies target two theoretical aims. One of these is designed to induce endogenous repair by upregulating resident brain-derived neural stem cell (NSC) niches within the adult brain and stimulating adult hippocampal neurogenesis, which is particularly important in the early stages of the disease. Nevertheless, this approach failed in clinical trials probably due to the ineffectiveness of the procedure to functionally compensate for the lost hippocampal neurons or because the method does not adequately address other features of the disease[58-60].

The other design is exogenous cell therapy, aiming to restore the neuronal networks using native or induced production of neuroprotective growth factors as contributers, based on the fact that the production of neurotrophins, which are factors supporting the growth and survival of neurons, is low in AD patients. Moreover, differentiation and participation of the stem cells in repopulating regions of

degenerated neurons can lead to therapeutic restoration[58].

The types of stem cells used in cell therapy are highly important from the points of providing unique distinctive cells required and for their different abilities to promote neurotrophic factors. In general two major stem cell types exist. One type is pluripotent stem cells including embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). The other type is adult stem cells which comprise NSCs, hematopoietic stem cells (HSC), mesenchymal stem cells (MSCs), and olfactory ensheathing cells (OECs)[61].

ESCs are capable of unlimited self-renewal. They are a perfect choice for cell replacement therapy, when their pluiropotency is precisely arranged into necessary neuronal types. Nevertheless their use is largely limited due to ethical concerns. Induced PSCs produced from fully differentiated somatic cells provide an opportunity to deliver patients specific pluiropotent cells suitable for autologous transplantation[62]. There have been successful trials with iPSC-derived cholinergic neuronal precursors, iPSC-derived macrophage-like cells, and iPSC-derived NSCs[63-65]. It seems that the niche of stem cell is very important in stimulating the differentiation of transplanted cells toward a special type from the point that some beneficial immunological or biochemical effects become possible. Use of neurotrophins leading to a shift from proinflammatory to anti-inflammatory cytokine reactions and use of proteins causing apotransferrin release from the cells are good examples of this phenomenon[64,66]. Both adult NSCs and adult MSCs can be affected and expanded with extrinsic chemical agents and growth factors[61,67]. Both are effective through replacement of degenerated cells and release of neurotrophic factors enhancing neurogenesis, such as vascular endothelial growth factor, brain-derived neurotrophic factor (BDNF), insulin growth factor-1, nerve growth factor (NGF), and fibroblast growth factor 2 (FGF2). In addition to enhancing neurogenesis, these secreted neurotrophic factors promote Aβ clearance, reduce tau hyperphoshorylation, enhance synaptogenesis, modify innate and adaptive immune cell responses by upregulating neuroprotective cytokines and decreasing proinflammatory cytokines, increase microglial phagocytic activity, enhance neovascularization, and modulate autophagy pathways[68-74]. Both NSCs and MSCs can be genetically improved to increase the success of transplanta-tion and to enable delivery of more efficient therapeutic and neurotrophic factors[75,76]. Several investigations have clearly shown that exogenous transplanted NSCs migrate precisely and may differentiate into various types nerve cells [61]. MSCs can be derived from a variety of adult tissues and organs, comprising peripheral blood, bone marrow, umbilical cord, amniotic fluid, Wharton jelly, fetal liver, muscle, lung and adipose tissue[77]. MSCs have been a good option in practice due to their high potency of proliferation, anti-inflammatory features, easy accessibility, high capability of propagation *in vitro*, secretion of an extensive range of cytokines, and absence of ethical problems. They can be administered intravenously, which is the least invasive method making multiple injections possible[61]. Additionally, MSC-extracellular vesicles (MSC-EVs), especially genetically modified ones, may be a new horizon in the treatment of AD. EVs are membrane vesicles that are secreted by various mammalian cell types, and have been demonstrated to deliver biologically effective molecules to neighbouring diseased or harmed cells, stimulating immune modulation, angiogene-sis, neurogenesis, and synaptogenesis. They also modulate physiological or pathological processes by echoing the genetic profile of their parent cell to recipient cells[78]. MSCs can be genetically modified to secret EVs supplied with therapeutic agents like growth factors and small interfering RNA (siRNAs) that target useful enzymes to the brain[79,80]. OECs are another source of multipotent stem cells found in the lamina propria, generally supporting neurons in structural, metabolic, and trophic aspects through secretion of neurotrophic growth factors (*e.g.*, NGF, BDNF) along with extracellular matrix molecules like fibronectin. By this way, OECs causes a synergistic effect for other transplanted stem cells. Genetically modified olfactory bulb-NSC/NPCs expressing hNGF showed beneficial effects on cognitive decline caused by ibotenic acid-induced lesions[81].

To increase the efficacy of stem cells and to protect them from the hostile microenvironment in AD, transplanting self-assembling proteins as three dimensional scaffolds or optimising structures for encapsulating stem cells using the techniques of tissue engineering and nanotechnology are highly recommended for the treatment of AD. Likewise there are some successful trials of these methods in animals and humans[82-89].

There are several phase 1 or phase 1/1b clinical trial studies with positive results using various methods such as transplantation of microencapsulated implants of genetically modified retinal pigment epithelial cells and autologous fibroblasts genetically programmed to produce NGF[86,87,90]. A recent study performed with human umbilical cord blood (hUCB)- derived MSCs on nine mild-moderate AD patients showed no adverse effects and no significant clinical efficacy or neurop-

rotective effect[91]. Currently, several phase 1 or 2 studies in humans are ongoing (Table 2). Stem cell treatment seems promising especially with the possible use of genetically modified stem cells and application of different tissue engineering techniques.

ADDITIONAL MODALITIES ON THE WAY

With the increase in knowledge about the fundamental mechanisms of gut microbiota affecting the brain through the immune system, endocrine system, vagus nerve, and bacteria-derived metabolites, some newer therapeutic approaches such as microbiome transplant can be developed[92-94]. Modulation of the vagus nerve, being in close contact with the gastrointestinal tract, has the ability to regulate mood and the immune system and may be another possible therapeutic modality[95,96].

Microglia-related pathways are also found to be related to the pathogenesis of AD based on emerging genetic and transcriptomic studies[97-101]. In the very early stages of the disease, microglia are active in synaptic pruning and in the regulation of neuroplasticity[102,103]. In the advanced stages, reactive microglia and astrocytes engulf amyloid plaques and secrete some pro-inflammatory cytokines. The recent observations that the blockade of PD-1 immune checkpoint decreases the pathology of AD and improves memory in mouse models of AD are promising and inspiring for the future [104-106]. New opportunities in the treatment of AD will arise with more studies, leading to better understanding of the role of microglial dysfunction as related to immunity, synaptic prunning, and neuroplasticity[104-109].

The early studies targeting mitochondria and bioenergetics as related to glucose hypometabolism of the brain in AD have shown promise in preclinical stages, but have not been successful in clinical trials[110,111]. However, this is still an important area of investigation aiming to develop new treatment measures.

CONCLUSION

It is accepted that there is need for new treatment modalities and effective combinations of these modalities. A foundation for effective approaches seems to be only possible with better understanding of the pathophysiology in relation to the stages of the disease and accurate follow-up of the disease with sensitive and comprehensive biomarkers. Using different biomarkers related to different aspects and stages of the disease will foster more plausible therapeutic strategies and assessment of outcomes.

While performing trials based on different therapeutic modalities, it will continue to be important to give careful attention to the relationships among cells within the brain and to the relationships between the brain and other organ systems.

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Table 2 Current clinical trials on stem cells

Clinical Trials. gov identifier	Type of stem cell transplantation	Study phase	Estimated number of participants	Status
NCT02054208	Intraventricular administration of hUCB-MSCs	1/2a	45	Recruiting
NCT02672306	UCMSCs	1/2a	16	Active, not recruiting
NCT02833792	Allogeneic hMSCs	2a	40	Recruiting
NCT02600130	Allogeneic hMSCs	1	30	Recruiting
NCT03117738	Autologous adipose tissue derived MSCs	1/2	60	Recruiting

UCB-MSCs: Umbilical cord blood-derived mesenchymal stem cells; UCMSCs: Umbilical cord mesenchymal stem cells.

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