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A Review of the Pharmacological Treatments of Alzheimer's Disease (AD)

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ABSTRACT

Alzheimer's disease (AD) is an irreversible, neurodegenerative disease that has haunted millions of lives globally. This article briefly reviews the diagnosis and pathophysiology behind AD while focusing on the currently approved and potential pharmacological treatments for AD. Cholinesterase inhibitors and NMDA receptor antagonists have been the most widely used drug to treat AD for decades. In 2003, Aducanumab was authorized by the US FDA for market use but not by other countries. Unfortunately, all the drugs mentioned could only ameliorate the clinical syndromes of AD instead of curing the disease and came with various side effects. Research has shown that the clinical progression of AD happens in parallel with the accumulation of amyloid β plaques and the spread of neurofibrillary tangles composed of hyperphosphorylated tau. There are many potential drugs under different stages of trials, including β-secretase inhibitors, γ-secretase inhibitors, monoclonal antibodies, tau aggregation inhibitors, and other therapeutic strategies. Although they are still immature to be put into clinical use, we are looking forward that a specific and efficient drug that has fewer side effects for AD will be developed in the future.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that accounts for about 80% of all dementia diagnoses (Hey et al., 2018; Weller & Budson, 2018). According to Alzheimer's disease international, dementia currently has more than 55 million patients living worldwide, which is estimated to triple by 2050 (Alzheimer's Disease International, 2021). AD is clinically characterized by progressive impairments in cognition, language, memory, and personality, which affects an individual's ability to perform basic tasks during daily life. Consequently, taking care of patients with AD is quite difficult and strenuous (Weller & Budson, 2018). This review aims to give a summary of the pathophysiology behind AD. It focuses on existing treatments and drugs targeting AD while also introducing some potential drugs that may be put into clinical use in the future and the challenges they currently face.

Diagnosis

Initially, when Alois Alzheimer first discovered the disease in 1906, the diagnosis of Alzheimer's disease was only confined to the presence of dementia (Scheltens et al., 2021). Nowadays, based on clinical data, we understand that the development of Alzheimer's disease forms a continual spectrum, with mild cognitive impairment being the intermediate stage between absolutely no syndrome and overt dementia (Scheltens et al., 2021). The identification of more than 40 Alzheimer's disease-associated genetic risk loci, including the APOE alleles, with genome-wide association studies and whole-genome and whole-exome studies, has also made genetic prognosis possible (Reitz, 2015; Scheltens et al., 2021). The diagnostic criteria of Alzheimer's disease have

changed from a purely pathological approach to a more comprehensive approach with various technologies. The development of an A(amyloid), T(phosphorylated tau), and N(neurodegeneration) framework that systematically groups biomarkers into three categories greatly facilitated the classification of the disease stages (AlirezaAtriMD, 2019). For instance, amyloid-positron emission tomography(amyloid-PET) is most useful in directly diagnosing the presence of AD, whereas 18FDG-PET can differentiate the extent of neurodegeneration (Rhodius-Meester et al., 2020). Brain MRI, on the other hand, can produce detailed images of brain atrophy and other tissue abnormalities, making it a powerful tool for revealing AD's progress (Chandra et al., 2019).

Pathology and Pathogenesis

The most prominent pathological features of AD are amyloid β(Aβ) plaques and neurofibrillary tangles. Amyloid plaques are the extracellular aggregation of Aβ40 and Aβ42 as by-products of APP metabolisms, whereas neurofibrillary tangles are constituted by hyperphosphorylated tau. (Lane et al., 2018). Although the pathogenesis of AD is still controversial, the most prevalent amyloid hypothesis suggests that the earliest progression of AD pathology involves an imbalance between Aβ clearance and Aβ production, which is performed through sequential cleavage of amyloid precursor proteins (APP) by β- and γ-secretase. Meanwhile, the Aβ pathology seems to stabilize at the preclinical stages of the disease (Scheltens et al., 2021). At the cellular level, abnormalities in neurons, microglia, and astroglia occur in parallel with the accumulation of Aβ, leading to neuroinflammation, vascular aging, and dysfunction of the glymphatic system (Dennis J Selkoe, 2016; Marta Cortes-Canteli 2020). The later spread of neurofibrillary tangles composed of tau is thought to be a downstream process induced by amyloid plaques; it is responsible for most of the severe clinical features of Alzheimer's disease, including loss of synapses and neurons (Long & Holtzman, 2019).

Currently Approved Pharmacological Treatments

Several treatments have been approved for market use. Although they do not cure or slow down AD progression, these drugs can alleviate some of the symptoms. Cholinesterase inhibitors and N-methyl-D-aspartate receptors include several drugs that have been approved for market use. Aducanumab is a drug that has only been approved in some countries, hence will not be discussed in this section. Several drugs will be discussed below with respect to their mechanism of action, possible side effects, and efficacy on AD (see Table 1).

Table 1. Current approved pharmacological treatment for AD

Drug name	Status	Possible side effect	Other use
Cholinesterase inhibitors			
Donepezil	Approved	Nausea, vomiting, diarrhea, muscle cramps, weight loss, loss of appetite, headache, confusion, etc.	Parkinson's disease, dementia with Lewy bodies
Rivastigmine	Approved		Parkinson's disease
Galantamine	Approved		Unknown
NMDA receptor antagonist			
Memantine	Approved	dizziness, confusion, aggression, depression, headache, sleepiness, diarrhea, constipation, nausea, etc.	Vascular dementia
Immunotherapy			
Aducanumab	Approved in the US	Diarrhea, falls, headache, confusion, dizziness, swelling of body parts, etc.	Unknown

Cholinesterase Inhibitors

An important manifestation of Alzheimer's disease is the loss of cholinergic basal forebrain (CBF) neurons, leading to declined neurotransmission, making cholinesterase inhibitors a plausible treatment(Mangialasche et al., 2010) . Some of the approved cholinesterase inhibitors include Donepezil, rivastigmine, and galantamine. However, there are many possible side effects, including gastrointestinal discomfort, fatigue, muscle cramps, and in severe cases, the worsening of cognition (Briggs et al., 2016). The targeting disease stages can vary depending on the specific agent used, with Donepezil being applicable to all stages. The overall effects are moderate, with about one-third of the users reporting no benefit and one-fifth reporting more considerable benefits. Meanwhile, it is estimated that the drug is not tolerable to around one-third of the patients due to side effects (Birks & Harvey, 2018).

NMDA Receptor Antagonist

Memantine is an agent that noncompetitively blocks the N-methyl-D-aspartate receptor and is thought to be neuroprotective by preventing neuronal loss (Keating, 2006). It is more tolerated than cholinesterase inhibitors, but side effects, including somnolence, constipation, and headache, can still occur. Unlike cholinesterase inhibitors, memantine demonstrated modest influence on moderate to severe AD, and there has been insufficient evidence to support its benefits in milder stages (Briggs et al., 2016; McShane et al., 2019).
Unfortunately, the overall effects of cholinesterase inhibitors and memantine are not as efficient as people expected and are too insignificant to make a huge difference. Some have proposed that the loss of CBF neurons and cholinergic transmission may act too far downstream in the neurodegenerative process of AD for there to be any plausible treatment. Thus, many researchers have focused on the rather upstream pathological processes (Mufson et al., 2008).

Potential Future Pharmacological Treatments

Amyloid-targeting drugs

The amyloid hypothesis describes a cascade of reactions that leads to the aggregation of Aβ, whose accumulation and deposition play a key role in AD (Scheltens et al., 2021). Such a hypothesis provides anti-amyloid drugs with the potential to become effective treatments for AD. There are primarily three types of anti-amyloid drugs with respect to their targets: targeting on β-secretase, targeting on γ-secretase that participated in the cleavage of APP, or directly targeting on Aβ aggregation. (Briggs et al., 2016).

β secretase (BACE) inhibitor

The inhibition of BACE can restrain AD progression by limiting Aβ production. There have been several different drugs that entered clinical trials. For example, LY2886721, a small-molecule nonpeptidic BACE1 inhibitor, was developed as an advancement of LY2811376. It was reported to be safe and well tolerated at first but was terminated in phase 2 clinical trials due to liver abnormalities (Ghosh & Tang, 2015). AZD3293, another BACE1 inhibitor, successfully entered phase 3 clinical trials and showed good tolerability in elderly AD patients in 2016. Nevertheless, the trials were terminated in 2018 because of their inefficacy (Athar et al., 2021). Verubecestat (MK-8931) and elen-becestat (E2609) demonstrated promising results in early clinical trials, which is why these two drugs managed to enter phase 3 clinical trials. Yet the trials were still terminated due to safety efficacy concerns (Alzforum, 2019b; Blume et al., 2018). Abecestat (JNJ-54861911), a thiazine-based small molecule, is a nonselective oral BACE inhibitor evaluated in phase 2/3 clinical trials. The results revealed dose-dependent

cognitive worsening and neuropsychiatric adverse events (Sperling et al., 2021).

γ secretase inhibitor

The inhibition of γ-secretase is vital to treating AD as it hinders the sequential cleavage of APP, thus reducing the production of Aβ. Semagacestat (LY450139) is a small molecule γ-secretase inhibitor that once entered phase 3 clinical trials. Nevertheless, studies were quickly halted in 2010 because patients had shown an apparent cognitive decline, along with an increased incidence of skin cancer (Doody et al., 2013; Folch et al., 2016). The possible reason is that γ-secretase catalyzes other transmembrane proteins, including the Notch receptor, which can lead to heavy splenic and hepatic consequences if inhibited (Yiannopoulou & Papageorgiou, 2013). Other γ-secretase inhibitors, such as Agavaceae, also showed discouraging results in treating AD (Athar et al., 2021).

Drugs Targeting Amyloid Aggregation

Aiming at amyloid deposition directly is another common approach to AD. Tramiprosate and colostrinin are two drugs that performed outstandingly during early clinical trials (Athar et al., 2021). Tramiprosate prevents the formation of β-sheet by reducing glycosaminoglycan binding to Aβ, whereas colostrinin prevents amyloid aggregation by provoking an innate immune response. All the same, neither of the drugs demonstrated promising results in later clinical trials (Hey et al., 2018; Sochocka et al., 2019). Interestingly, GV 971 (Sodium oligomannurarate), another inhibitor toward amyloid aggregation, was invented and approved for treatments of mild to moderate AD in China, while it is still undergoing phase 3 clinical trials in the US (Green Valley (Shanghai) Pharmaceuticals Co., 2021).

Immunotherapy

Immunotherapy can be categorized into Active and passive immunization (Athar et al., 2021). Active immunization involves producing a vaccine to target the production of amyloid plaques. However, the best performing vaccine so far, AN1792, was terminated at phase 2 clinical trials due to 6% of the subjects suffering from meningoencephalitis (Stephen R Robinson 1, 2004). Passive immunization relies on monoclonal antibodies and polyclonal immunoglobin to remove amyloid plaques. Among all the related agents such as Bapineuzumab and Solanezumab, Aducanumab is the most pivotal and worth discussing drug as the FDA has approved it on 7th June 2021, for the treatment of AD (Dr. Patrizia Cavazzoni, 2021). Although failed in phase 3 randomized, double-blind, placebo-controlled, parallel-group study earlier, Aducanumab showed promising effects in reducing amyloid plaques in another phase 3 trial, which led to the approval of the drug (Dhillon, 2021).

Tau-Targeting Drugs

Hyperphosphorylation and tau deposition are found in AD patients' brains and possibly cause synaptic loss and neuronal death, which play an important role in AD pathology. Naturally, drugs have been developed to target Tau (Briggs et al., 2016). As it is another pathological characteristic of AD, scientists also regard tau as a target, attempting to develop drugs that will modulate the phosphorylation of tau with inhibitors and/or promote aggregation disassembly. Studies illustrated possible efficacy in the future; however, until now, there still hasn't been any drug approved by the FDA for the treatment of AD. LMTM, Blarcamesine, Saracatinib, and other drugs are still being evaluated, with some reaching phase 3 clinical trials (Athar et al., 2021).

Multi-Target Drugs

AD itself results from sophisticated interactions between multiple pathological pathways, yet all the currently approved drugs for AD exhibit only one target. Therefore, attention has been shifted to multi-target drugs (MTDs) capable of aiming at more than one target (Thiratmatrakul et al., 2014). For instance, Ladostigill acts as a cholinesterase inhibitor and a monoamine oxidase enzyme. Another drug Idalopirdine inhibits acetylcholinesterase while targeting 5-HT6 receptors (Alzforum, 2019a; Atri et al., 2018). Yet despite MTD being a promising and rational approach to AD, there hasn't been an approved drug on the market.

Conclusion

Alzheimer's disease is a devastating and burdening disease well known for its irreversibility and progressive nature. In the past, little was known about the disease, which largely restricted the invention of new drugs and therapies. Nowadays, however, with a further understanding of the disease from a molecular level, several novel approaches to tackle the disease have been proposed and studied extensively. After decades of research, cholinesterase inhibitors and NMDA receptor antagonists are still the only two types of drugs against AD that are approved and prescribed on a large scale. Aducanumab has only been approved by some countries for market use. More importantly, these drugs cannot solve the underlying cause of AD and are not tolerable for every patient as they might result in severe side effects. β secretase inhibitors, γ secretase inhibitors, monoclonal antibodies, tau aggregation inhibitors, and other therapeutic strategies have presented encouraging results. However, none of the drugs have passed clinical trials due to concerns regarding inefficacy and safety issues. Further research is still imperative to significantly reduce cognitive loss, slow down the disease progression, and eventually discover a cure for Alzheimer's disease in the future.

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