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2. Alzhiemers Disease: Review On Methods Of Treatment

Priyanshu Kumar Srivastava*, Dr Ashish P Anjankar**, Dr. Gaurav Vishal***

**Medical Student, Jawaharlal Nehru Medical College,Datta Meghe Institute of Higher Education and Research, Sawangi, Meghe,Wardha, India*

***Department of Biochemistry, Jawaharlal Nehru Medical College,Datta Meghe Institute of Higher Education and Research, Sawangi, Meghe,Wardha, India*

****MBBS, MD, Bokaro General Hospital (BGH), Jharkhand, India*

Abstract

This review article presents an update on the clinical and physiological phase of Alzheimer's disease, risk factors with the focus on strategies for its prevention, followed by treatment limitations. Alzheimer's disease is a frequent neurodegenerative disorder around the world and is becoming a potential health concern in the coming years. Numerous therapeutic strategies have been proposed and explored but a cure is yet to be discovered and priority remains its prevention.

Prevention strategies can significantly slow down the onset of Alzheimer's disease. Due to the difficulty of delivering drugs to the central nervous system, current pharmacological treatments only address symptoms. However, a number of studies have demonstrated that the use of nanoparticles, specifically exosomes and nanoliposomes, as a novel therapeutic approach for brain bioavailability have been conducted. These studies have also demonstrated that these nanoparticles can function as an intelligent drug delivery system to cross the blood-brain barrier and reach the brain's target tissue.

Key Words: *Alzheimer's Disease, Therapeutics Strategies, Polyunsaturated Fatty Acids, Blood–Brain-Barrier, Liposomes, Exosomes, Intranasal Administration*

Introduction

Because of population aging and lifestyle changes, a large number of affected individuals, the toll of such diseases take on the lives of people and their loved ones, neurodegenerative disorders (ND) provide a significant contemporary health concern. Millions of people around the world suffer from neurodegenerative disorders today(over 50 million); if no practical preventive or therapeutic measures are discovered, the numbers will keep on increasing (may cross 150 million by 2050). In 60% to 80% of cases, Alzheimer's disease is diagnosed as the neurodegenerative illness.[1]

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The exact origin of the disease is not known till date and no remedy has been developed for over more than a century. Alzheimer's disease has been classified into two types:- 1. The sporadic form, also known as sporadic Alzheimer's disease(SAD) and 2. The genetic form, also known as autosomal-dominant AD (ADAD), it does not affect more than 1% of cases and manifests before the age of 65. The chances of having SAD increases by two times every five years and often strikes those over the age of 65. Here, the Alzheimer's disease that occurs sometimes is covered. [2, 3]

AD disease is caused by aberrant protein aggregation in the nervous system and structural as well as functional damage to the central nervous system. In fact, two different types of lesions associated with AD have been found: 1) Neurofibrillary tangles formed by hydrophosphorylated tau proteins and
2) Amyloid plaques formed by beta-amyloid peptides.
A gradual process including biochemical, neurophysiological, neuroanatomical, and cognitive problems can be described as AD. Dysfunctions of dendrites, axon and synapses are brought on by the first oligomerization of soluble beta-amyloid peptides in the brain.[4]

Since soluble beta-amyloid peptide oligomers seem to represent a more pathogenic and toxic variant of beta-amyloid peptides,researches have been directed towards them for quite some time. Beta-amyloid peptide oligomers are pathogenic agents that manifest before the initial neuropathological indications of AD.[5] Subsequently, brain lesions appear gradually and are linked to the death of neurons in specific brain areas, however they do not show any symptoms.Memory loss and cognitive decline are signs of Alzheimer's disease that appear over time.[6]

Clinical studies made over a wide range of therapeutic techniques have only given medications that are symptomatic rather than curative. This has caused focus to shift toward AD risk reduction or prevention. Modifiable risk factors causes more than 30% of AD around the world.[7]

These variables offer potential targets for preventative treatments aimed at lowering the risk of AD and maybe neurodegenerative disorders in general. The main emphasis of current problems is to enhance the preclinical stage early illness detection. Lipid nutrients are essential for the brain and cognitive processes, as evidenced by several researches. Neuronal membrane components known as phospholipids are amphiphilic molecules that include omega-3 polyunsaturated fatty acids (n-3 PUFA) in the brain.They may play a neuroprotective role in synaptic plasticity and neuron function, as

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several studies have shown.Dietary techniques that focus on PUFA can be utilized to optimize the lipid state of the central nervous system, as food is a significant source of these fats. [8]

Breaking the blood brain barrier of the CNS for delivering therapeutic molecules to the target brain tissue is another obstacle in treating AD. The blood-brain barrier forms shielding of the the CNS from numerous therapeutic molecules and harmful pathogens, it also restricts access to the CNS. The usage of nanoparticles, with range in size from 10nm to 1000nm are able to encapsulate therapeutic compounds by focusing on CNS transport pathways, can enhance the ability of molecules to pass the blood-brain barrier (BBB) and arrive at specific brain areas.[9]

One of the most efficient drug delivery methods for protecting therapeutic chemicals and getting them to the target tissues are soft nanoparticles like exosomes or nanoliposomes (NL).[10] Nanoliposomes have a restorative effect at the cellular level and higher tissue levels of neurological illnesses such as stroke, Parkinson's disease, AD, implying enhanced NP-mediated bioavailability in the central nervous system. To enhance the bioavailability of PUFA in the form of NL, nanotechnology can also be applied. NLs are small spherical, closed vesicles formed by phospholipid bilayers scattered in an aqueous media .Plurilipids rich in n-3 PUFAs and with advantageous neuroprotective characteristics can be engineered into NL.[11]

Furthermore, many different compounds, such as hydrophilic or hydrophobic medications, proteins, or DNA, can be encapsulated using NL.Given that their biofilm properties closely mimic those of cell membranes, they constitute an excellent drug delivery mechanism. Furthermore, NL forms a barrier that shields the molecules from being broken down by bile acid, digestive fluids, oral and stomach enzymes, and intestinal microbes. The present work examines the physiopathology and clinical features of social anxiety disorder (SAD), taking into account research models of AD. It then delves into the current treatments that target strategies for prevention and the novel applications exosomes and NL, to lower the risk of AD.[12]

Discussion

Recent advancements for treatment of Alzheimer's disease

In order to slow the course of cognitive symptoms as well as behavioural and psychosocial symptoms of dementia, current medication treatments for Alzheimer's are mainly symptomatic and not curative (BPSD). Four medications—galantamine, rivastigmine, memantine, and donepezil—belong to the

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anticholinesterase inhibitor and anti-glutaminergic groups and are authorized for sale. Oral or transdermal administration are the methods used to provide these therapies.[13] The purpose of anticholinesterase inhibitors is to raise the brain's acetylcholine levels, which are involved in memory and information transfer between specific neurons. The goal of these therapies is to address the acetylcholine shortage seen in AD patients' central nervous systems. N-methyl-D-aspartate (NMDA) receptors have a noncompetitive antagonist action that is exploited by anti-glutaminergics to control glutamate levels. Glutamate is a neurotransmitter involved in memory and learning processes in the brain. Elevated glutamate is probably going to have pathogenic effects, including neuronal death. These medication-based therapies aim to slow down the progression of the illness, stabilize or temporarily enhance cognitive abilities, and manage behavioral issues. These therapies assist AD patients and their carers maintain their independence and enhance their quality of life, even though they are not curative. Nevertheless, these therapies merely address the symptoms of AD rather than its underlying cause, and their efficacy is only marginal at best before the process of neurodegeneration begins, these pharmacological treatments might be more advantageous in the early asymptomatic period.[14] The limited efficacy of these treatments is also attributed to other factors, such as the challenge of brain drug targeting because of the BBB's restricted passage from the circulation to the central nervous system. In fact, permeability problems at the BBB in AD cause a lot of medication studies to fail. [15]

This makes the higher dosage required, which may also raise the risk of other undesirable consequences. [16] A number of techniques have been proposed to address the challenge posed by the BBB for CNS medication delivery. Preclinical research may not always take age related changes in neuron membranes and neuron membrane receptors into account, which could potentially lower drug efficacy. In example, alterations in the microdomains of synaptosomes isolated from elderly mice were seen in a recent study , which enhanced the synaptosomes' sensitivity to amyloid stress and hindered the ciliary neurotrophic factor's neuroprotective effects. [17]

Treatments may also be limited if they are administered in the latter stages of the disease. For example, testing of anti-amyloid immunization to eradicate amyloid plaques have been done in animals with ADAD genetic mutations which cause an early and rapid accumulation of amyloid plaques. [18] Nevertheless, a reduction in amyloid burden was shown in multiple human clinical studies employing this strategy, but neither a noteworthy clinical benefit nor a decrease in disease progression

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was observed. Therefore, it's probable that the treatments are less successful because they're given when Alzheimer's is already in an advanced stage. Prompt intervention could be crucial, underscoring the need for improved early-stage AD diagnosis with new biomarkers. [19] Target populations with risk factors, such as family history and isolated memory complaints, should in reality be considered for a prompt and precise diagnosis. While amyloid plaque formation has been the focus of drug development, other novel targets still need to be investigated.The lack of effective, curative treatments and the difficult accurate diagnosis of AD in its early stages highlight the need for neuroprotective and preventive strategies to slow down neurodegenerative process involving neuronal dysfunctions in axons, dendrites, synapses, and lower the risk of the disease. Gene therapy in Alzheimer disease. [20]

Gene Therapy for Alzheimer's Disease

Recombinant adeno-associated viruses (rAAVs) and gene therapy have recently advanced, opening the door to the potential of treating these disorders in humans. Ten patients with early AD were treated with NGF gene ex vivo or in vivo therapy by Tuszynski et al. (2015) in an attempt to assess the capacity to degenerate neurons in AD towards a nervous system growth factor (NGF).The results showed that neurons exhibited a positive response, including activation of functional indicators, axonal sprouting, and cell hypertrophy.[21] NGF-induced sprouting was produced by growth factor therapy and remained safe for ten years following gene transfer. In a different study, scientists introduced the gene PGC1-alpha (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha) into mice's brains using a modified virus, which inhibited the disease's progression. Following four months of injection, the mice receiving treatment showed reduced amyloid plaques, no loss of hippocampal brain cells, and enhanced memory. Multiple plaques were present in the brains of those who had not received treatment.[22] The planning of this investigation was based on previous findings regarding PGC-1α, which showed that the same group was able to reduce the amount of amyloid-β (Aβ) produced in cell culture. The outcomes of a multicenter randomized clinical trial using intracerebral gene therapy in individuals with Alzheimer's disease (AD) were recently published.[23]

This study proved that sham surgery-controlled stereotactic gene transfer trials in AD patients are feasible. Although it was possible and well-tolerated, adeno-associated virus vector (serotype 2)-nerve growth factor (AAV2-NGF) distribution produced no therapeutic results. Thus, validation of the specific gene targeting is needed for the investigation in a recent breakthrough.

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The importance of therapeutics in Alzheimer's

The newest technique is called "theranostics," which integrates diagnostics and therapies rather than utilizing them separately. Theranostics has the potential to fundamentally alter both AD diagnosis and current therapy. Gold nanorods combined with two known Aβ inhibitors (Aβ15–20 and polyoxometalates) may recognize, inhibit, and destroy the resulting Aβ aggregates by exposing them to near infra-red light. The absorbance of gold nanorods varies based on the Aβ aggregation process, allowing for the tracking of the disease's progression.[24] Phenothiazine derivatives have been produced and function as near-infrared fluorescent probes. These probes can detect amyloid plaque in the brain and retinal tissue of transgenic mice because they have a high affinity for it. These substances have the ability to break down pre-formed Aβ fibrils and prevent the accumulation of Aβ plaque.[25] Charged molecules, which show enhanced fluorescence after binding, are very attractive to Aβ aggregates. By effectively stopping the aggregation of Aβ1-40 and Aβ1-42 fragments, it offers treatment for AD. A blood brain barrier shuttle that binds to Aβ fibrils has been created via recombinant design using the antibody mAb158. Two single chain variable segments of transferrin receptor antibody-8D3 are fused with this antibody.[26] It is well recognized that 8D3 improves brain uptake. This fusion allows the shuttle to selectively penetrate the blood brain barrier and distribute mAb158 to the brain, which functions as both a radioligand for PET imaging and an Aβ immunotherapy, assisting in the therapy's evaluation at the same time. There is always an overabundance of metal ions, which are act as catalysts for plaque formation.[27] Based on this finding, researchers created a nanoprobe that, when exposed to 980 nm, can detect the concentration of copper by including the chelator 8-hydroxyquinoline-2-carboxylic acid. Chelators increase the structural change of Aβ and prevent apoptosis triggered by amyloid plaque by capturing excess copper ions in the brain.[28] Incorporating Congo red/rutin into iron oxide magnetic nanoparticles, these particles can be used for controlled medication release, oxidative damage prevention, and magnetic resonance imaging-based amyloid plaque detection. Personalised medicine may soon benefit from the field of theranostics, which use a single chemical substance for AD diagnosis and therapy.

Quantum dots, which are fluorescent nanoparticles, are also used in theranostics. Their distinct optical and electrical characteristics are the cause of this. QDs are extensively utilized in diagnostics and imaging. This is due to the fact that one wavelength may be used to measure emission from many QDs concurrently in a single experiment. Theranostics applications of QDs, where simultaneous imaging, diagnosis, and therapy are conceivable, have attracted a lot of interest recently. [29]

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Xiao et al. (2016) used glycine-proline-glutamate-coated graphene quantum dots (GQDs) in APP/PS1 transgenic mice. Strong promise as a treatment for AD was demonstrated by the reduction of amyloid plaque formation and the increase in anti-inflammatory cytokines while pro-inflammatory cytokines increased.[30] Low level lasers, which have wavelengths between 632.8 and 400 nm, can be used to lower oxidative stress and inflammation in a variety of medical diseases. However, because relatively little light really enters the brain, this treatment is ineffective. This issue can be resolved by utilizing a method known as "Bioluminescence Resonance Energy Transfer to Quantum Dots" (BRET-Qdots). In animal studies, these CdSe or CdTe quantum dots alleviate oxidative stress and inflammation caused by amyloid plaque by acting as a source of near-infrared light. Additional applications for low-level laser therapy (LLLT) include the treatment of various illnesses involving oxidative stress disorders and inflammation. A sensitive technique based on simultaneous electrochemical and fluorescence detection of APOE4 DNA—the gene linked to Alzheimer's and coronary artery disease—was reported by Mars et al. (2018). Because of its extremely sensitive fluorescence capabilities, curcumin was employed for its dual-sensing transducer response. The electrochemical response was improved by the use of graphene quantum dots. The presence of several APO e4 DNA targets was sensitively reduced, as indicated by the analytical reaction. This was caused by the hindered photo-electron transfer activity brought on by the creation of DNA complex. The curcumin-GQDs system was also studied in the clinical fluid due to its great selectivity and effectiveness. The relative standard deviation (c.a.) for the DNA target in human blood plasma was 4.7%, according to the data. The relative standard deviation (c.a.) for the DNA target in human blood plasma was 4.7%, according to the data. As quantum dots are very new, it is a relatively new endeavor. Current scanners are limited in their ability to acquire fluorescent signals under the proper excitation levels for red and green lasers. With ApoE serving as a model analyte, Morales-Narvaez et al. (2012) investigated the biosensing capacity of QDs (QD655) and a fluorescent dye (A647) used in the sandwich ELISA as reporters in microarray format and compared it with a traditional ELISA. A small amount of human serum was needed to perform the test with excellent accuracy and great sensitivity. The detection of ApoE multiple isoforms and other AD biomarkers is suggested to use this concept. In a different work, Medina-Sanchez et al. (2013) employed zinc-sulfide/cadmium-selenide QDs as labelling agents for ApoE test and detection. For the purpose of purifying and concentrating samples, they used them in a magnetic zone using magnetic beads.It is feasible to construct integrated, portable, tiny, and reasonably priced systems with these specifications. [31]

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Non-Medicinal Treatments

Neurodegenerative illnesses can also be treated non-pharmacologically, as an alternative to pharmacological therapy.[32] A number of completed and ongoing international trials and research, examine the use of several activities in the multidomain intervention in AD.[33] Increased physical activity, cognitive training, better nutrition, and a reduction in the rate of cognitive and functional decline as well as the severity of BPSD are all positively correlated, according to study. However, there is little evidence available on long-term research because these activities have only been conducted for brief periods of time.

Methods of Preventing Alzheimer's Disease

A review from another article emphasizes the interest in non-drug preventative therapy, especially for MCI or the preclinical stage. As was previously mentioned, AD abnormalities such endosomal pathway blockage or Abeta-induced synaptic dysfunctions start early and continue over decades, perhaps even decades, before the existing therapies start to show very small benefits.[34] Due to changes in the structure and function of brain, the reduced cognitive performance starts to decline around the age of 45 and increases with aging.[35] Determining modifiable risk factors is crucial to developing preventative measures against this sneaky illness.

Dietary interventions

This is because lipids are important for brain structure and function, and because optimizing lipid status through diet is relatively simple.[36] Nutritional Management Omega 3, 6, and 7 fatty acids PUFA is essential for energy generation and storage, cell membrane formation and fluidity, and enzymatic activity, among other processes. Because the body cannot produce these particular PUFAs—linoleic acid and alpha linolenic acid, which can only be obtained through diet—they are necessary. Arachidonic acid, eicosapentaenoic acid, and DHA are all precursors of LA and ALA. Brain integrity, function, and development all depend on PUFA. [37,38,39] DHA, an n-3 fatty acid, is abundant in the brain and is mostly found in the membranes of synaptic clefts and photoreceptors. It is mostly found in phosphatidylcholine (PC) in lower proportions, as well as in the membrane phospholipids (PL) of phosphatidylethanolamine (PE) and phosphatidylserine (PS). One of the important function of DHA is neuroprotective and syanaptic plasticity.[40] It has a significant impact on aging, memory, vision, and corneal nerve regeneration. N-3 PUFAs and lipids in the brain are made up of DHA. Gray matter has very high amounts of it. As people age, their total gray matter volume decreases, which is correlated

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with a drop in DHA concentration.[41] Numerous physiological and cellular processes, such as myelination, neuroinflammation, neuronal differentiation and development, membrane fluidity, and neurotransmitter release, are influenced by DHA. Long-chain n-3 fatty acid supplementation has shown encouraging promise in the early phases of AD. Studies show a link between food and cognitive decline associated with aging. [42]

Fish oil has been investigated as a possible dietary supplement for AD prevention and is a great source of DHA. Nonetheless, it appears that the only individuals with improved cognitive outcomes following fish oil treatment are those with moderate impairment in cognition that does not carry the APOE ε4 mutation.[43] This would imply the significance of n-3 FA supplementation, particularly in individuals who are at risk, prior to the start of AD symptoms. In fact, in the early stages of AD, DHA can attenuate molecular pathways that are harmful to the central nervous system. A significant contributing factor to AD may be the alteration in the fluidity of neuronal membranes that occurs with brain aging. Dietary supplements containing DHA may be able to stop age-related alterations in neuronal membranes and the resulting deficits. DHA may also be more beneficial when combined with other therapies, such as neuroprotective molecules, than when taken alone. This is due to the fact that DHA supplementation may increase sensitivity to molecular therapeutic targets—like ciliary neurotrophic factor—that are lacking in AD. (CNTF). Numerous studies carried out in vivo and in vitro have demonstrated that DHA can offer neuroprotection against the neurotoxicity caused by Aβ.[44] Frther evidence of DHA's ability to minimize AD risk comes from studies that suggest it can enhance blood flow, reduce inflammation, and lower Aβ generation in a variety of AD models. [45, 46]

A number of clinical studies are now being conducted to evaluate the neuroprotective benefits of n-3 PUFA supplementation in AD patients. In terms of cognitive or neural improvement, the outcomes in AD patients have not been consistent despite so many trials. Furthermore, the effects are often transient. A number of variables, including as the use of a different formulation of DHA or the administration of DHA solely in late-stage AD, may contribute to these variations in age-influenced bioavailability.

The method of delivering bioactive compounds to the central nervous system (CNS) in AD is extremely intricate, and creating preventative and treatment plans is difficult. New approaches to enhance the penetration of chemicals into the central nervous system are being tested via research.

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The foundation for developing drugs for combination therapy is not well-established. In order to maximize the synergy of effects, agents may advantageously target complementary features of the illness or the same route and multiply the impact. It makes sense to evaluate individual combination therapy components in animal model systems to confirm their efficacy, and to investigate potential synergistic and additive effects of the combination as a whole. A compound's failure in an animal model would be one factor in the decision to stop developing it.

Analyzing combinations on animals would also make it possible to find any potentially significant drug-drug interactions or combo toxicity. Additionally, information on drug-drug interactions, safety, and tolerability in humans will be required from phase I first-in-human studies. Target engagement and dosage data for each component and combination would be produced via phase II learning studies. Phase II permits the investigation of dosage and dose-response; in combination regimens where synergies are applicable, lower doses of individual medicines may be employed. This result might contribute to reducing the possible toxicity linked to combinations. Confirmatory phase III studies would be carried out if phase II results were positive. The benefit of having the candidate agents at the same degree of inquiry when combinations become appropriate is having the combination tactics planned from the start. One such way to fill a pipeline of combination therapies is using combinations of new medicines and better-understood repurposed drugs. In combination treatment regimens, targets such as tau, Aβ, inflammation, and neuroprotection may be addressed.

It is helpful to get a quick overview of current therapies before delving into the specifics of innovative therapy approaches for managing AD. A number of pharmacological medications have long been developed to counteract the worsening impact that AD has on a person's memory and cognitive abilities. The first use of these medications was predicated on the cholinergic and glutamatergic theories. One of the earliest theories to be suggested to explain.

First-generation stem cell types, known as mesenchymal stem cells (MSCs), are extracted from adult tissues such as muscle, adipose tissue, and bone marrow. Because of their trophic, immunomodulatory, and anti-inflammatory qualities, MSCs have been employed in clinical studies (Kimbrel and Lanza, 2020). The discovery of pluripotent stem cells (PSCs), which are second-generation stem cell types, has completely changed the field of stem cell research since PSCs may transform into any type of cell in the.

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Two-dimensional culture system

Stem cell-based models of AD have been extensively used in research on potential treatment approaches. According to Ostalek et al. (2017), iPSC technology may include personal data and offer a platform for creating novel therapeutic strategies. Rapid exploration of cellular pathophysiology, including transcription, genetics, and signalling pathways, can be facilitated by the highly scalable 2D co-culture methods using iPSCs. [47]

Human-animal chimaeras for AD

The nuances of human pathophysiology are too complicated for any one model to accurately capture. Mice and non-human primates are good examples of animal models that benefit from living biological systems. Animal models are frequently employed in preclinical AD research in order to better understand graft function, integration, and innervation in the host. Therefore, before using stem cell-derived therapy in human trials, preclinical animal research should address its inherent problems. [48]

Enhancement of cell therapy efficacy in animal studies

Although preclinical research with animal models and cell replacement treatment has demonstrated the anticipated outcome, its efficacy is restricted. Improvements in the transplanted cells' long-term survivability and differentiation efficacy should lead to the development of more inventive and novel medications. [49]

Clinical trials on cell replacement therapy for AD

The majority of cell replacement therapy clinical studies that have been completed or are currently in progress for AD employ MSCs from various sources as their therapeutic agents (Table 2). As of right now, no stem cell therapy has advanced to phase 3 in AD clinical trials. The results of the first study have been investigated in order to assess the safety, tolerability, and effectiveness of transplantation. In 2015, allogeneic hUCB-MSCs were injected into the right precuneus and hippocampal regions of participants in a phase 1 clinical study. [49]

Immune injection cell therapy

The identification of the lymphatic system of the central nervous system (CNS) suggests that graft rejection after allogeneic cell and tissue transplantation may not be completely prevented (Louveau et al., 2015, Parmar et al., 2020). AD disease is initiated and exacerbated by the neuroimmune system

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(Hickman et al., 2018). Refocusing on the topic of immunological rejection in cell replacement therapy is crucial. [49]

Ethnic problems related to stem cell-based therapies

Stem cell transplantation is now being seen as a way of treating Alzheimer's disease.. However, ethical concerns regarding cell replacement therapy should be supported by scientists and ethics bodies (Farahany et al., 2018). Any position taken on these issues must be ethically justified. Even though the development of iPSCs and MSCs has greatly settled ethical disagreements over therapeutic application, several ethical issues still require extensive scientific investigation. [49]

Therapeutic scenario

As we previously indicated, a preventive trial design may be the optimal treatment setting for cell therapy for AD (Fig. 3). This drug can reduce transplant rejection by using autologous cells rather than allogeneic cells. Autologous cells produced from patients can be utilized to evaluate tailored medications using disease-in-a-dish models that contain patient-specific data. Engrafted cells may become resistant if genetic corrections or alterations are made prior to transplantation.s[49]

Conclusion

Due to its complexity, treating AD patients is still challenging. The only approved treatments for Alzheimer's disease at the moment are memantine and cholinesterase inhibitors, or these two medications combination. Moreover, a number of novel medications that showed early promise have since failed bigger phase III studies due to non-attainment of effectiveness objectives. The main reason for the high failure rate of alzhiemr therapies in development are the pathology that causes of AD, our incomplete understanding of different pathways involved in the development of the disease and the causing neurodegeneration, and since the current treatments are not effective. Though the combination of memantine and cholinesterase inhibitors has not shown much promise in treating AD, targeting several pathways might be essential for a successful course of treatment. Therefore, more research into rational agent combinations should be done.

DMTs or symptomatic treatments are being studied in a number of current clinical studies as supplements to baseline standard-of-care medication. Nonetheless, a chance to treat the illness that could have synergistic effects is presented by a combination of at least two drugs that target different pathways, and there aren't many of them in clinical trials. Lower dosages of the various treatment

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drugs may be possible when they are combined, which would cut expenses and adverse effects. New designs through clinical trials can cause new methods for therapy along the course of illness progression. For instance, dementia, early-stage AD, and preclinical AD may all benefit from a different combination of medications. The difficulties in treating AD have influenced treatment approaches in a variety of ways, such as the effective co-administration of two agents that target distinct pathways concurrently, as evidenced by successful treatment regimens for other severe illnesses and conditions like HIV and cancer; the development of novel medications as supplemental treatments to standard care; and the repurposing of already-approved medications for other therapeutic conditions.

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