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REVIEW PAPER

Current Knowledge about Alzheimer's Disease and Biological Therapies as Promising Hope for its Treatment

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative illness whose incidence is expected to increase in the coming years. Different studies have been done to have a better understanding of its pathophysiology and thus determine possible treatments. Some traditional options include pharmacological therapies, lifestyle-related therapies, and Comprehensive Psychoestimulation Programs. However, no current option can prevent or delay it, and existing ones have many side effects. Biological drugs are considered a hopeful alternative. They suppress the pathology complications and reduce the adverse effects to a greater extent. Within the biological medicines investigated to treat AD in recent years are monoclonal antibodies and cell and gene therapy. Only aducanumab and lecanemab (human monoclonal antibodies) are currently approved. The others are in the clinical and preclinical research phases. For this reason, investigations should continue to allow its prompt application on AD and other disorders that affect an appreciable percentage of the world's population.

Keywords: *Alzheimer's disease, biological therapy, monoclonal antibody, cell therapy, gene therapy.*

INTRODUCTION

Neurodegenerative diseases are characterized by progressive dysfunction and neuron death in the Central Nervous System (CNS). This degeneration occurs in neurons with specific functions, determining the clinical picture. [1] Alzheimer's disease (AD) is a progressive neurodegenerative pathology that is the leading cause of dementia, becoming one of the most lethal and costly illnesses. [2] In 2015, it was estimated that around 47 million people worldwide suffered from it. Furthermore, this figure is expected to rise to 130 million by 2050 due to the progressive population aging and the life expectancy increasing. [3]

AD irreversibly affects memory, thinking, language, and self-judgment. [4, 5] Advanced age is the principal risk factor associated. [5] Moreover, it is characterized by two main

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biomarkers: extracellular amyloid-β plaques and neurofibrillary or tau tangles. [2, 4, 5]

In recent decades, multiple studies have been conducted to comprehend its pathophysiology better, identify risk factors, and propose possible treatments. [2, 6] Some of the traditional therapies include pharmacological options such as acetylcholinesterase (AchE) inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists. [7] Likewise, lifestyle-related strategies comprise physical exercise, calorie restriction, a Mediterranean diet, [8] and Comprehensive Psychostimulation Programs (CPP). [9] Nevertheless, no practical approaches prevent or avoid progressive development.

For this reason, in recent years, biological drugs have been presented as a hopeful alternative to this condition. [7, 8] A biological medicine is one whose active ingredient comes from a biological source or living organism. [10, 11, 12] It involves cells, tissues, organs, cells, and fluids (blood and plasma) of human or animal origin, microorganisms (such as bacteria or yeast), and biotechnological cellular designs. [13] Vaccines, allergens, certain hormones, cytokines, monoclonal antibodies, enzymes, and gene and cell therapies are within the pharmacological groups. [13, 14]

Monoclonal antibodies [5] and gene and cell therapies [8, 15] have been studied as possible AD treatments. Therefore, the research aim is to summarize the biological therapies available until 2024 to treat this condition.

GENERAL ASPECTS OF ALZHEIMER'S DISEASE

To better understand AD, it is necessary to establish aspects of the CNS anatomy and functioning. The CNS is made up of a cranial and a vertebral part. The cranial one is divided into the frontal, parietal, occipital, and temporal lobes, corresponding to the cranial bones related to their location. Fissures or sulci separate them. [16]

The frontal lobe is responsible for voluntary eye movements, speech, memory components, and cognitive functions, including concentration, reasoning, abstract thinking skills, and socially appropriate behavior. The temporal, parietal, and occipital lobes meet in the interpretive area. Damage to this zone can decrease cognitive functions. [16]

In addition, the CNS is constituted of glial and neuronal cells. Glial elements metabolize, release, and respond to neurotransmitters and modulators and control the microenvironment around neurons. They play an essential role in the lymphatic system, responsible for cerebrospinal fluid flow and eliminating potentially neurotoxic waste products such as amyloid-β peptide. Neurons are the main component of the nervous system, capable of receiving, processing, integrating, and transmitting electrical or chemical signals through the synapses formed between them. [17]

The amyloid-β peptide, under normal conditions, is produced as a soluble monomer, circulating in low concentrations in cerebrospinal fluid and blood and acting as a neuroprotectant and neurotrophic factor. However, its insoluble deposits are one of the first causes of AD because of its neurotoxicity and the release of free radicals. [18]

Another relevant compound is the tau protein, a macromolecule associated with microtubules. It mainly allows its association, dissociation, and dynamism in neurons, maintaining the cell shape and transport pathway through the axons. Besides, the phosphorylations in its structure generate several isoforms. These variants affect their interaction with proteins and microtubules, causing the formation of aggregates or deposits related to neurodegenerative pathologies. [19, 20]

Regarding AD, it is a common neurodegenerative brain disorder in people over 65 years of age. It generates progressive cognitive decline with accompanying functional impact, affecting memory and the ability to think and do simple tasks. [4, 21] Additionally, the person may become lost in familiar places and experience complex behavioral changes. This scenario is occasioned by the loss of connections between the brain neurons responsible for the microcircuit formation and maintenance that support learning, memory, and other cognitive functions. [22] Moreover, it can originate dementia, [23] leading to the patient's death due to starvation, malnutrition, or pneumonia. [24]

PATHOPHYSIOLOGY

Dementia, a result of higher functions global disintegration in the CNS, [25] is anatomically characterized by brain atrophy, particularly in the entorhinal cortex and the hippocampus. These crucial brain areas, when atrophied, lead to progressive memory loss and inability to perform daily activities (learning). [26, 27]

As a complement, it has been described that the patient may suffer a transparency decrease and leptomeninges fibrosis, [28] which surround the CNS and fulfill a protective function. [29] In addition, it can show a decrease in brain weight, affecting both hemispheres and producing global, bilateral, and symmetrical atrophy. Atrophied gyri and increased sulci are primarily denoted. [28]

Although AD has an unknown cause, it is believed that its etiology may be multifactorial. [26] Risk factors such as a sedentary lifestyle, smoking, hypertension, dyslipidemia, diabetes, and obesity play a relevant role. [26, 30]

A small percentage of cases with genetic origin are called familial AD. It is characterized by earlier development (about 10 to 12 years earlier) compared to the idiopathic or sporadic form. In it, there is a history of dementia in more than 80 % of the cases. Therefore, a genetic component is suggested as a risk factor. [26, 28] A genetic element is the apolipoprotein E (APOE) gene presence, [28] whose function involves maintaining the apolipoprotein particles' structure and regulating their metabolism, [31] becoming a risk factor for the late-onset, especially when allele 4 has a frequency almost equal to allele 3. If APOE4 occurs heterozygously, the disorder onset happens five to 10 years earlier than expected, and when it arises homozygously, between 10 and 20 years before. [28]

Furthermore, alpha-2-macroglobulin mutations are being investigated as a risk factor for late-onset because it is present in 30 % of these individuals. [28] Alpha-2-macroglobulin is a macromolecule with an antiprotease function. [32]

The pathology can be classified into two stages: [33]

- Preclinical stage: the result of the markers is unknown, but it is developing without symptoms.
- Clinical stage: the disease progresses, and there is evidence of markers.

In the preclinical stage, there is a division between the presymptomatic and asymptomatic at-risk states. [33, 34] The asymptomatic persons at risk are difficult to define since they do not generate any signs or symptoms but have at least one of the markers as positive. [33]

Meanwhile, presymptomatic individuals have genetic factors such as the APOE4 allele and amyloid precursor protein (responsible for amyloid-β metabolism) presence or presenilin-1 and presenilin-2 mutations, causing accelerated amyloid-β peptide production. [35-38] These elements promote its development.

Currently, two theories try to explain the cognitive deficits generated by AD: cortical disconnection and cholinergic. [28]

Cortical disconnection theory

It establishes neurofibrillary degeneration in the entorhinal cortex, which is distributed in the neurofibrils of layers II and IV so that the hippocampus is isolated from the neocortex. Thus, there is a deficiency of neuropeptides such as glutamate (a primary excitatory neurotransmitter in the brain and spinal cord), neuropeptide Y (promotes food intake, provokes vasoconstriction, and acts on heteroreceptors in postganglionic sympathetic nerve endings to reduce norepinephrine release), oxytocin (causes contraction of the uterus smooth muscle), vasopressin (increases permeability of the kidney collecting ducts so that water enters the hypertonic interstitium of the renal pyramids, provoking urine concentration and volume decrease), and somatostatin (with effects on sensory input, locomotor activity, and cognitive function). [28, 39]

Such a panorama is correlated with aphasia (language trouble characterized by communication inability or difficulty), apraxia (inability to execute coordinated movements without a physical origin reason), and agnosia (inability to recognize information arriving through the senses). It also does the same with visuospatial and executive disorders. [28, 40]

Cholinergic theory

A significant diminution of over 90 % in AchE activity is observed in advanced stages, leading to a profound cholinergic system compromise. The selective degeneration of the nucleus basalis of Meynert (principal origin of cortical cholinergic innervation), the septal nuclei (from the hippocampus, the axons synapse in this part, although their function is not well known), and the diagonal band of Broca (cholinergic neurons are situated in this area), located in the cerebral cortex and the hippocampus, causes a progressive anterograde memory deficit. [28, 41, 42]

Table 1 shows the imbalances in other neurochemical pathways that explain the non-cognitive symptoms in AD. [28]

Table 1. Imbalances in other neurochemical pathways that explain the non-cognitive symptoms of AD. [28]

Condition	Result
Serotonin deficiency	Depressive symptoms, obsession, compulsion, and aggression.
Norepinephrine deficiency/increase	Depression (in case of deficit) and psychomotor agitation (in case of increase).
Acetylcholine deficiency	Cognitive impairment, mainly with memory problems.
Dopamine relative conservation	Choline/dopamine imbalance with the relative increase of the latter, with hallucination generation, sleep disorders, and psychosis.

EPIDEMIOLOGY

In 2005, it was estimated that 24.2 million people were living with dementia, and 4.6 million new cases were reported each year. North America and Western Europe showed a higher prevalence in the population at 60 years old (6.4 and 5.4 %, respectively), followed closely by Latin America (4.9 %), China, and the developing countries of the Western Pacific (4.0 %). [30] Likewise, in 2013, it was estimated that 44 million people suffered from this illness worldwide, with 7.6 million new cases annually. [43]

By 2021, estimates reached around 50 million people globally, with almost 10 million new cases annually. [44] According to studies, the number of individuals with this problem will double every 20 years to reach 115.4 million in 2050, augmenting more significantly in developing regions. [45, 46] As a complement, according to the World Health Organization (WHO), between 60 and 70 % of dementia cases are present as AD. [47]

Incidence studies of dementia and AD coincide in showing that people are more likely to undergo as they age, with an exponential growth pattern after 65 years old. [3] However, it is necessary to clarify that it is difficult to establish precise incidence rates because of the trouble in determining the onset age and defining a disease-free population. [30]

High blood pressure, cardiovascular disease, diabetes, dyslipidemia, smoking, obesity, and traumatic head injuries are among the factors that raise the possibility of suffering from it. For their part, education, leisure, the Mediterranean diet, and physical activity reduce the predisposition. [30] **Table 2** shows factors that can modify the probability of having AD and its possible mechanisms.

Table 2. Factors that modify the risk of suffering from AD. [30]

Antecedent	Probability of disease suffering	Possible mechanism
Arterial hypertension	Increase and decrease	Microvascular disorder
Cardiovascular disease	Increase	Parenchymal destruction and amyloid-β deposition
Type II diabetes		Cerebrovascular effect and competition between insulin and amyloid-β for clearance
Smoking		Cerebrovascular effects and oxidative stress
Obesity		Increased risk of type II inflammatory diabetes
Traumatic head injury		Increased amyloid-β and deposition of amyloid precursor protein
Education	Decrease	Provides cognitive reserves
Leisure		Improves lipid metabolism and mental stimulation
Mediterranean diet		Provides antioxidant and anti-inflammatory effects
Physical activity		Activates brain plasticity and promotes vascularization

TRADITIONAL TREATMENTS

Pharmacological therapies

AchE inhibitors such as donepezil, rivastigmine, and galantamine are administered. These molecules rise cholinergic transmission, improving patients' symptoms. [48]

Improvement has been demonstrated throughout six to 12 months. The three drugs approved for mild-to-moderate AD cause adverse effects such as nausea, vomiting, diarrhea, weight loss, insomnia, and bradycardia. [34]

Moreover, modulators of glutamatergic transmission are administered, specifically memantine. It is an NMDA receptor antagonist whose mechanism involves glutamate receptor inhibition. Such amino acids generate excitotoxicity and neuronal death. [49]

This medication is approved for moderate to severe illness, administered alone or with AchE (34). Studies have shown that it only acts if glutamate levels are abnormal. All populations, including older adults, tolerate it, and the most common unwanted reactions (mild-to-moderate) comprise vertigo, headache, and hallucinations. [50]

On the other hand, cerebrolysin has evidence of acting positively in mild-to-moderate AD. It is a peptide with neurotrophic action derived from porcine brains that decreases the phosphorylation of the amyloid precursor protein and modulates GSK3β and CDK5 in the transgenic mouse. [34] However, it is classified as an investigational agent because it lacks studies and conclusive results.

Other drugs with little information are statins. They are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A and reduce cholesterol levels, whose high values intensify the AD risk. [8] Still, two extensive studies examined the effects of cognitive deterioration but did not demonstrate consistent benefits. [51] Thus, they are not recommended for prevention or treatment. [34]

Additionally, patients need psychotropic medications such as antidepressants and antipsychotics to treat behavioral problems in 70 to 90 % of cases. Aspects such as the effects of sedation, falls, or amnestic disorders must be considered. Benzodiazepine employment significantly alters behavior. For this reason, the United States Food and Drug Administration (FDA) advises against their administration in dementia cases. Other agencies, such as those in Canada, Spain, and the United Kingdom, mentioned risperidone can be facilitated for up to six weeks. [34]

Non-pharmacological therapies

Pharmacological therapies do not exclude non-pharmacological interventions. These are based on the brain's plasticity (neuroplasticity), which is how it adapts to new situations and regains balance after an injury. [9] They improve non-cognitive symptoms, maintain dignity and communication, reinforce self-esteem, and increase quality of life. [34] Plasticity depends on intrinsic and extrinsic factors, where environmental influences are cataloged in the latter factors and are the basis for applying these procedures. It improves neuroplasticity, slows the evolutionary process, and stimulates higher mental functions. [9]

During the CPP, a cognitive psychostimulation workshop, a psychoexpression workshop, and an occupational workshop are held. The results demonstrate a general improvement in two to four months, especially in people with subcortical dementia. Nonetheless, patients with vascular dementia and AD have benefited from its implementation. This program focuses on serving the individual regarding their interactions in activities, emotions, autonomy, and abilities, along with integrating their family and environment. [9]

All of the above shows that current therapy is scarce. AchE inhibitors are the reference treatment, while adjuvants include acetylcholine synthesis precursors, NMDA receptor antagonists or modulators, and antioxidants. [52] The latter substances are indicated because they can capture free radicals and coordinate with metal ions associated with neural plates, evidencing beneficial neuroprotective effects. [53]

These options provide the patient with palliative measures, reducing agitation and memory loss and improving quality of life. [53] Still, cognitive degeneration processes progress irreversibly, so other options, including biological therapies, have been sought.

BIOLOGICAL THERAPIES

They are those whose active ingredients come from a biological source, [10] such as cells, tissues, organs, fluids (including blood and plasma), which can be of human or animal origin, microorganisms (such as bacteria or yeast), and biological cell designs. These occur naturally or in the laboratory, reflecting the variability inherent in living materials. [13, 14] Within the pharmacological groups are antigens, allergens, vaccines, cytokines, monoclonal antibodies, enzymes, and cell and gene therapies. [14]

As mentioned above, conventional treatments fail to suppress AD progression and generate distinct side effects. Therefore, biological therapies aim to suppress the severity associated with this disorder. [54] The options are explained below.

Monoclonal antibodies

Antibodies or immunoglobulins (Ig) are glycoproteins that recognize the antigen at the B cell membrane, generating a response and activating more B lymphocytes and other immune cells capable of attacking said antigen. [55]

They have four polypeptide chains (two heavy and two light), which create a Y-type structure, as seen in **Figure 1**. Both are subdivided into a constant and a variable region. The latter, known as the antigen binding fraction (Fab), promotes antigen recognition and binding. For its part, the constant region or crystallizable fraction (Fc) has effector functions of antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). [56, 57]

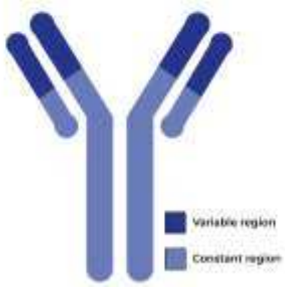

Figure 1. General structure of an antibody.

Antibodies are classified into five isotypes or classes: [58]

- IgA: it exists in two forms. The monomeric one circulates in the blood, and the dimeric form is abundant in biological secretions (colostrum, milk, bile, and saliva).
- IgD: it is present on the surface of B lymphocytes and promotes cellular differentiation.
- IgE: most molecules are fixed in the blood basophils and the submucosa mast cells of the urinary, respiratory, and digestive systems.
- IgG: it is made up of two heavy and two light chains.
- IgM: it has a pentameric structure, which allows complement activation to a greater extent through the classical pathway.

Monoclonal antibodies are specialized glycoproteins produced by B lymphocytes, capable of recognizing a single antigen or specific epitope. [55] There are four types: murine (from mice), chimeric (murine sequences are replaced by human antibody sequences, specifically the constant region), humanized (90 % of the genetic material is of human origin), and fully human (100 % of sequences come from the human being). [55, 56] By a suffix assigned to each protein's name, its origin can be known. For murine antibodies, it corresponds to -momab, while for chimeric, humanized, and fully human ones, it is -ximab, -zumab, and -umab, respectively. [56]

Anti-amyloid-β monoclonal antibodies have been obtained from murine models and subsequently humanized. [5] Immunotherapy is a treatment for inducing, suppressing, or enhancing the patient's immune response. The therapy could be active (inducing a humoral immune response) or passive (administering anti-amyloid-β antibodies). [59]

Anti-amyloid-β monoclonal antibodies

Aducanumab

Aducanumab is a fully human IgG1, approved by the FDA in 2021. [60] It is specific for insoluble fibrils and soluble oligomers of amyloid-β proteins, decreasing the levels dose-dependently and breaking through the blood-brain barrier. [61]

Side effects include headache and diarrhea. [62] The major disadvantage is associated with amyloid-related imaging abnormality edema (ARIA-E), shown up on magnetic resonance imaging (MRI) as sulcal effusion or brain edema, and amyloid-related imaging abnormality hemorrhage (ARIA-H), with superficial siderosis and microhemorrhage. [63]

Its approval has generated substantial controversy. This situation is because phase III clinical trials failed to improve the AD symptoms significantly. [62]

Bapineuzumab or AAB-001

It is a humanized IgG1 derived from a murine monoclonal antibody 3D6. The molecule binds to the N-terminal residues of amyloid-β in a monomeric helical conformation, causing its selective binding to fibrillar and soluble species. [64]

In a phase II, open-label extension (OLE) study, the long-term safety and efficacy were evaluated in individuals with mild-to-moderate illness. Those between 58 and 78 years of age who completed any of two randomized, placebo-controlled, double-blind studies (subcutaneous single-dose-escalation or intravenous multiple-ascending-dose) entered the open-label extension investigation were considered. Three groups were evaluated: bapineuzumab or placebo subcutaneous (SC) and bapineuzumab intravenous (IV) in OLE (monoclonal antibody SC/monoclonal antibody IV), bapineuzumab (IV) in

Study 201 and OLE (monoclonal antibody/monoclonal antibody), and placebo in Study 201 and bapineuzumab IV in OLE (placebo/monoclonal antibody). It should be noted that study 201 was a phase I, randomized, double-blind, 16-week placebo-controlled study. [65]

Of the 194 patients enrolled, 30 withdrew due to adverse effects and 85 due to personal decision (total withdrawal: 158). In this trial, no significant difference between the early and delayed treatment groups was seen in cognitive and functional decline. [65]

Additionally, new security issues were not reported. Most people described at least one emerging adverse effect, the most common being falls, urinary tract infections, and agitation. There was also ARIA-E in 22 patients, where the highest incidence occurred in those exposed to the drug for the first time in the open-label extension study compared to those who had been previously exposed. [65]

Regarding phase III studies, a three-year extension of two double-blind placebo-controlled investigations sought to evaluate the molecule's long-term safety, tolerability, and maintenance of efficacy in patients with mild-to-moderate AD dementia. In this multicenter research, the 1462 individuals (688 APOE4 carriers and 774 non-carriers) received IV infusions (0.5 or 1.0 mg/kg) every 13 weeks without knowing whether they had received the drug or the placebo in the previous studies. [66]

Among the most frequent side effects, falls, urinary tract infections, agitation, and ARIA-E appeared in a number greater than or equal to 10 % of the individuals. The incidence rate of ARIA-E was higher among carriers and non-carriers who were administered bapineuzumab for the first time in that trial compared to those who had been previously exposed. Likewise, it was concluded that the infusion every three weeks for three years was well tolerated, with tolerability and safety profiles like those found in previous research. [66]

Solanezumab

Solanezumab is a humanized IgG1 that binds to the amyloid-β peptide's mid-domain and increases soluble amyloid-β clearance. [67, 68, 69]

In two phase III, double-blind trials, with 1012 and 1040 individuals with mild-to-moderate AD enrolled, placebo or solanezumab (400 mg IV) was administered every four weeks for 18 months. Both investigations did not show significant improvement in the scores on the 11 or 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale from baseline to week 80. Besides, the incidence of ARIA with edema or hemorrhage was 0.9 and 4.9 %, respectively, for the glycoprotein. [69]

Gantenerumab

It is another monoclonal antibody in phase III. Unlike solanezumab and bapineuzumab, this protein is the first fully human anti-amyloid-β monoclonal antibody of the IgG1 type, which binds to a conformational epitope expressed on amyloid-β fibrils. [70, 71]

Among the studies, a randomized, double-blind, placebo-controlled phase III investigation evaluated the drug over two years. The 797 enrolled persons received 105 or 225 mg of the protein or placebo every four weeks by subcutaneous injection. Unfortunately, the trial was stopped early because the objectives could not be achieved. Nevertheless, the incidence of dose-dependent effects exhibited in exploratory analyses suggests that higher dosing may be necessary to achieve the clinical efficacy required. [72]

As a complement, a randomized, placebo-controlled, multi-arm trial of solanezumab or gantenerumab in people with dominantly inherited AD across asymptomatic and symptomatic stages was done. Mutation carriers were distributed 3:1 to either medication or placebo, and the treatment was administered for four to seven years. Fifty-two persons received gantenerumab, 52 solanezumab, and 40 a placebo. Both drugs engaged their amyloid-β targets, but neither demonstrated a beneficial effect on cognitive measures compared to controls. The solanezumab-treated group showed more cognitive decline on some measures, while gantenerumab significantly reduced amyloid plaques and cerebrospinal fluid total tau protein, among other biomarkers. Regarding adverse effects, ARIA-E was appreciated in 19.2, 2.5, and 0 % of the gantenerumab, placebo, and solanezumab groups, respectively. [73]

Ponezumab

It consists of a humanized IgG2 monoclonal antibody that binds to the amyloid-β C-terminal epitope, specifically to residues 30 to 40. IgG2 antibodies have a lower propensity to induce immune effector function than IgG1, reducing this protein level in patients with mild-to-moderate AD. [71]

Concerning research made, 36 individuals with cerebral amyloid angiopathy (ages between 55 and 80 years) participated in a phase II, randomized, double-blind investigation for 90 days. They received ponezumab (24 participants) or placebo (12 participants). The drug was given at 10 mg/kg on day 1, followed by 7.5 mg/kg on days 30 and 60. The main results show one asymptomatic occurrence of ARIA-E in the ponezumab group, and the final number of new cerebral microbleeds from baseline to day 90 did not differ between groups. Additionally, the ponezumab group had a participant who suffered non-fatal new cerebral hemorrhage with aphasia and a participant with subdural hemorrhage that site investigators deemed to be non-drug related. Nonetheless, it was safe and well tolerated. The ponezumab group did not show the expected improvement. [74]

Another study from this phase did not reveal clinical efficacy, so the molecule was discontinued. [71]

Crenezumab

It is an IgG4 antibody capable of reducing the microglia overactivation risk, as it minimizes Fc gamma receptor activation. In transgenic mice, it triggered less tumor necrosis factor-alpha (TNF-a) release and ARIA. It recognizes amyloid-β monomers, oligomers, and fibrils but has less affinity for the first. [70, 71]

Two phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety trials in participants with early AD (3736 and 3664 patients aged 50 to 85) were established to evaluate the glycoprotein efficacy and safety. They were randomly distributed in a 1:1 ratio to either drug (60 mg/kg IV every four weeks for up to 100 weeks) or placebo. Compared with previous research, new safety signals were not recognized, and ARIAs were rare, mild, and transient. Both studies were discontinued because although it was well tolerated, crenezumab did not reduce clinical decline in participants with early disorder. [75]

Lecanemab

It is the humanized version of murine mAb158, which selectively binds to amyloid-β protofibrils. Compared to aducanumab and gantenerumab, lecanemab binds more strongly to these protofibrils. Phase I trials demonstrated safety, and it was well tolerated at single doses up to 15 mg/kg and multiple doses up to 10 mg/kg biweekly. No severe side effects were found. [71, 76, 77]

An 18-month, multicenter, double-blind, phase III investigation was conducted for approval. The 1795 participants were randomly assigned in a 1:1 ratio to be treated with the antibody (10 mg IV/kg every two weeks) or placebo. The monoclonal antibody generated infusion-related reactions in 26.4 % of the individuals and ARIA-E or effusions in 12.6 %. Nevertheless, the drug reduced amyloid markers in early AD and showed less decline in cognition and function measures than the placebo at 18 months. The problem was that adverse events accompanied these benefits. [78] However, with this data, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee voted affirmatively that the study results verified the drug's clinical benefit for its treatment. [79]

Anti-tau protein monoclonal antibodies

DMR7 y SKT82

There are possible drugs to stop the spread of the tau protein, including DMR7 and SKT82. They are monoclonal antibodies that selectively bind to the misfolded protein structure. Specifically, they bind extracellularly to tau seeds, for example, AD-tau seeded recombinant tau preformed fibrils (AD-P1 PFFs), and inhibit internalization by a possible block in the binding receptors associated with it and the subsequent seeded fibrillization or aggregation. SKT82 has been more effective than DMR7. [61]

In a study with mice in which injections of the human protein induced the pathology, the binding of SKT82 and DMR7 to tau seeds was verified. Both inhibited its recapture in primary neurons and prevented the respective aggregation. [80]

ANTI-hTREM2 monoclonal antibody

AL002c

It is an IgG1 murine monoclonal antibody against the triggering receptor expressed on myeloid cells 2 (TREM2). TREM2 is a lipid receptor in microglia that promotes their survival and proliferation. Its decrease modifies the response to amyloid-β plaques and increases tissue damage, while overexpression declines the illness. AL002c acts as a TREM2 agonist, providing a neuroprotective effect to microglia, reducing neuronal and neurotoxic damage from amyloid-β plaques, as was seen in a trial performed with a mouse AD model. [81]

Cell therapy

Stem cells are undifferentiated cells that can self-renew (produce new stem cells) and differentiate into mature elements of diverse lineages under certain conditions. [15, 82] They can be classified according to their differentiation capacity or potential and origin. Based on their differentiation potential, they are categorized into four groups: totipotent, pluripotent, multipotent, and unipotent. [83]

Totipotent stem cells can be differentiated into embryonic tissue (ectoderm, endoderm, and mesoderm) and extraembryonic tissue (placenta, amnion, yolk sac, allantois, and chorion). For their part, pluripotent cells differentiate into any cells in the embryonic tissue, including sexual or germ cells. In contrast, multipotent cells generate those from their embryonic layer, capable of generating an entire organ (brain, skin, retina, pancreas, skeletal muscle, among others), whether in an embryo or an adult. Finally, unipotent stem cells specialize in one cell lineage. [83]

Moreover, according to their origin, they are classified into adult or somatic stem cells (whose differentiation process is irreversible after forming the three embryonic layers), embryonic stem cells (from the first phases of embryonic development and capable of promoting any cell type in the organism), [83] and induced pluripotent stem cells (IPSc), produced artificially and programmed to behave like embryonic ones by introducing reprogramming factors that induce pluripotency. [83, 84]

Adult stem cells

Adult stem cells are classified as multipotent and unipotent. They are found in adult tissues and the umbilical cord. Their functions include conserving and restoring the anatomical site in which they are located. [83]

Neuronal cells are indicated within adult stem cells. Nonetheless, their renewal capacity is limited, causing the search for other sources to replace the damaged ones. [7]

This cell type is utilized significantly because human embryo destruction is not required, reducing ethical and legal problems. Besides, they have the same plasticity as embryonic stem cells, which is essential for cell differentiation in medical treatments. Another advantage is that since they come from the same patient, the rejection problem by the person's immune system is avoided. [83]

Among them, mesenchymal stem cells have been evaluated in regenerative medicine due to the ease of isolating, expanding, and obtaining them from various sources such as adipose tissue, blood, bone marrow, and skeletal muscle. [15]

Wharton's jelly of the umbilical cord is an abundant source, and its collection process is painless. These cellular elements have immunomodulatory properties, high proliferative potential, and differentiation plasticity. Such characteristics surpass bone marrow mesenchymal stem cells. [85, 86] Therefore, they have been studied as a possible therapeutic tool to prevent neurodegenerative diseases, including AD. [87]

In a preclinical study with 11-week-old C57BL/6J mice, in which this condition was induced, the potential impact of human umbilical cord blood-derived mesenchymal stem cells on neuronal loss was examined. It was indicated that its intracerebral injection reduced the expression of glial activation markers, oxidative stress, and murine brain apoptosis, which implied improved learning and memory capacity. [87]

Similarly, in a preclinical study with transgenic mice, the immunomodulatory effects on neuroinflammation of mesenchymal stem cells systemic transplantation through the tail vein were studied. Histological analysis was performed to determine the number and size of pE3-amyloid-β plaque and glial distribution. A size reduction was observed, supporting that transplantation has an immunomodulatory effect on microglial cells. [88]

Embryonic stem cells

These cells are found in the blastocyst inner cell mass. They are pluripotent and can develop on different cell types. [15] Under certain appropriate culture conditions, they can be induced in cardiomyocytes, hepatocytes, and neurons, among others. For this reason, they have been studied as a cellular source for regenerative medicine.

A preclinical study investigated the production of cholinergic neurons from mouse embryonic stem cells and their potential for cellular restoration in an AD rodent model. Neuronal precursor cells were produced by selection with growth factors under serum-free conditions. Their behavior was evaluated when transplanted into rodent brains, and memory improvement was observed. [89]

Nevertheless, the utilization of embryonic stem cells involves a controversial ethical component. The discovery of iPSCs has countered this scenario.

Induced pluripotent stem cells

After years of research, in 2006, Takahashi and Yamanaka demonstrated that it is possible to reprogram human fibroblasts into iPSCs using four specific transcription factors (Oct3/4, Sox2, c-Myc, and Klf4). [84, 90, 91] They are introduced through retroviral vectors. [90] Another technique for cell reprogramming is somatic cell nuclear transfer. Through it, the somatic cell nucleus is transplanted into an egg cell without a nucleus. [83]

Cellular reprogramming is an emerging technology that has advantages over embryonic stem cells. As mentioned above, one is ethical, as the embryo's destruction is not required to acquire them. Another is that it is easy to obtain from patient-accessible somatic cells, such as skin fibroblasts, avoiding immunological rejection when transplanted. [15, 90]

In vitro research has shown that it is possible to convert human fibroblasts into neurons with a chemical mixture, such as a cocktail of small molecules, without going through a neuronal progenitor. For this, human fibroblasts were acquired from the foreskin of a 28-year-old man. They were treated in a neural induction medium with valproic acid. Seven days after treatment, a significant fraction of cells with typical neuronal morphology was detected, expressing characteristic cellular markers. [92]

Regarding clinical trials with cell replacement therapies as an option against AD, phase I and II trials have been performed or are in progress, most of which gathered mesenchymal stem cells from multiple sources. Still, there is no phase III research. [93]

One of the investigations was an open-label, single-center, phase I clinical trial. The aim was to evaluate the dose-limiting toxicity and safety of brain injection of human umbilical cord blood-derived mesenchymal stem cells. Nine people aged between 50 and 75 participated. Injections were administered at the hippocampus and the right precuneus level, both in low (three individuals received 3.0×10^6 cells/60 µl) and high doses (6.0×10^6 cells/60 µl). No volunteers exhibited severe side effects. The most common were wound pain after the surgical procedure, headache, dizziness, and postoperative delirium. Furthermore, dose-limiting toxicity was not determined. Thus, it was found that the administration was safe, feasible, and tolerable, with the consequent need to evaluate its effectiveness. [94]

Despite the many preclinical studies, there are few results in clinical studies where stem cell effectiveness is evaluated since the majority are active or the results have yet to be published. [95] Therefore, researchers must continue advancing toward these phases to understand the mode of action of the transplanted cells and the molecular mechanisms that govern regeneration and neuronal microenvironment.

Gene therapy

It consists of introducing genetic material into cells to modify the course of a medical condition through the reestablishment, introduction, or interference of a cellular function. The genetic material to be introduced can be natural genes, DNA fragments, or chimeric genes. [96] It can be done in germ lines, where the modified gene is transferred to the next generation, or in somatic lines, where transfer to the next generation does not occur. Currently, cell therapy is only allowed in somatic lines. [97]

This therapy uses *ex vivo* and *in vivo* techniques. In the first, the cells are modified *in vitro* to express the desired genetic information and are implanted in the recipient. In contrast, *in vivo* cell treatment employs vectors that express the desired information. [98]

Vectors can be viral or non-viral. Non-viral ones are liposomes, naked DNA, and DNA-protein complexes. They are preferred from a security perspective but have the drawback that they are less efficient in performing the required transfer. [96, 98] Therefore, viral elements such as retroviruses and adenoviruses are available. Retroviruses can insert genetic material into the genome of dividing cells and transmit it to their progeny. Nevertheless, it can only be inserted while dividing and can cause mutations if inserted randomly. [96]

In addition, adenoviruses can introduce it, even if the cells are not dividing, and they are safe. The disadvantage is that they have a short-expression time as the immune system eliminates them. [96]

It has been noted that PPARγ-coactivator-1α (PGC-1α), a transcriptional coactivator for the peroxisome proliferator-activated receptor-γ (PPARγ), has a potential neuroprotective effect. Its expression is decreased in AD. However, it has been observed in a murine model that with a stimulus through nicotinamide riboside, the synthesis increases, reducing amyloid-β levels and cognitive deterioration. [99]

For this reason, a lentiviral vector was formulated with the capacity to express human PGC-1α that had as target specific brain regions of transgenic mice. The study found that its administration prevents neuronal loss by increasing growth factor transcription and decreasing neuroinflammation caused by amyloid-β levels. [99]

Another study covered tau protein phosphorylation at threonine-205 (T205), as it provides a protective function. This process prevents complex formation with postsynaptic density protein 95 (PSD-95), mediating amyloid-β toxicity. The postsynaptic kinase p38γ, responsible for phosphorylation, was utilized in a murine model. An improvement was seen in the individuals of an AD animal model. [100]

Nerve growth factor (NGF) is another element because it regulates the functional state of brain cholinergic neurons. After an injury, it prevents death and promotes learning restoration. In a multicenter phase II trial, 49 participants with mild-to-moderate AD were randomly assigned in a 1:1 ratio to receive stereotactically guided intracerebral injections of adeno-associated viral vector (serotype 2)–nerve growth factor (AAV2-NGF) or sham surgery. The purpose was to determine if it was well tolerated and generated evidence of cognitive decline in mild-to-moderate AD with dementia. [101]

Although the treatment was well tolerated and no significant differences were defined between those who received the placebo versus the vector (10 % of patients showed an increase in anti-AAV2 antibodies, but anti-NGF antibodies were not detected), no significant variations were discovered in cognitive improvement. NGF may be a potential therapy for cholinergic preservation, but its impact on other elements related to the illness has not been demonstrated. [101]

CONCLUSIONS

AD has traditional pharmacological therapies that benefit the patient's condition, symptoms, and lifestyle. Accompanied by non-pharmacological therapies, good results have delayed the progression and improved cognitive function. Nonetheless, they do not stop such progression and generate numerous side effects.

Thanks to new technologies and research approaches, innovative alternatives have emerged to control this devastating pathology, precisely biological drugs. These options show comparative advantages, such as suppressing AD-associated effects and significantly reducing adverse events. These options include monoclonal antibodies and cell and gene therapy. Of all the medicines mentioned in this review, only two are currently approved: aducanumab and lecanemab, both monoclonal antibodies. The others are in the preclinical and clinical research phases.

This situation shows the progress and consideration of new therapies for diseases. Therefore, research must continue to allow its early application for the treatment of AD and other neurodegenerative disorders that affect a substantial percentage of the world's population.

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