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Alzheimer's Disease: New Treatment Perspectives Involving Active and Passive Immunotherapy

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Abstract

Alzheimer's Dementia is a Neurodegenerative Disease, which usually affects individuals over 60 years of age. In the patient's brain it is possible to identify the presence of neurofibrillary tangles and the deposition of senile plaques, respectively characterized by hyper phosphorylated tau protein and the accumulation of beta-amyloid proteins. Among the treatments recommended by the medical literature and the guidelines are acetylcholinesterase inhibitors, butyrilcholinesterase and NMDA glutamate receptor antagonists; However, they are unable to slow the progression of the disease, and do not prevent cognitive loss. Nevertheless, they can bring important improvement of the quality of life of the individual. In the case of an incurable disease, new studies are being done to prevent this cerebral degeneration using new techniques and the promise of promising treatments such as active immunotherapy (administration of synthetic protein anti-tau) and passive (administration of antibodies Monoclonal), although some of them are still in the test phase. According to the bibliographic review carried out and based on articles from the last ten years, the study was concluded with the positivity of the tests and with the promise of positive results.

Keywords: Alzheimer's Disease; Alzheimer's Disease Vaccine; Alzheimer's Disease Immunotherapy; Beta-Amyloid Protein; Tau Protein

Introduction

The Alzheimer's Disease (AD) was identified for the first time for the German psychiatric doctor Alois Alzheimer, being described as a progressive neurodegenerative disease, characterized by the loss of memory, besides cognitive impairments that could lead to death. Normally it assaults the individuals over 60 years old. According to estimates, in 2050 more than 25% of the world's population will be elder, increasing the prevalence of the disease, and prioritizing, like that, the emergence and use of new drugs I order to minimize the harm and damages or even avoid them [1,2].

The dementia type AD has a great impact on the economy, with world cost estimate in 818 billion dollars, and being foreseen an increase in this number to one trillion dollars until 2018 with its prevalence and incidence, showing an increase of 35% compared to 2010, according to estimates of World Alzheimer Report Updates 2015. This cost is even below Market values (billing) from companies like Apple (742 billion of dollars) and the Google (368 billion of dollars). It must be considered that the number of people that live with dementia double in every twenty years, growing to 74,7 million until 2030 and 131,5 million until 2050 (internet, 87 pages) [3].

The fragments of the tau and beta amyloid proteins join themselves, originating neurofibrillary tangles and senile plaques, respectively, cumulating in the cerebral cortex, with projections to the hippocampus, where the memory is filed (so preventing its formation) and then, they expand through other areas of the brain damaging the senses. The multiple stages from the disease are characterized by the progression and expansion of those plaques. The actual treatments visage to improve the life quality of the ill people, being more effective when used early, this is why the new studies consist in vaccines and monoclonal anti-bodies. to prevent the aggregation of those proteins [4]. The (Figure 1) shows the brain of a normal person and the brain of a person with Alzheimer's disease, highlighting the presence of protein aggregation plaques.

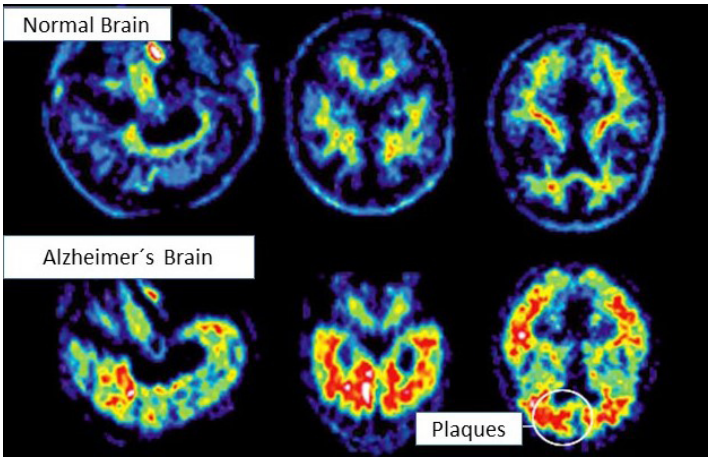

Figure 1: Images of patients with and without AD [5]. Source: Adapted from ALCALDE, 2014.

This article pursuit to identify the main researches in progress that will produce the new therapeutic alternatives to the Alzheimer's Disease, before the difficulties that the drugs used nowadays already present. It highlights the importance of the immunotherapy as a promisor treatment.

Methods and Materials

It is a study based on the literature review, conducted in the period between January and July 2017 and that had as its source of research the bases PubMed and Science direct. We considered the articles published in the last ten years and the keywords used in the search were: Alzheimer's Disease, Alzheimer's Disease Vaccine, Alzheimer's Disease Immunotherapy, Tau Protein, Beta-Amyloid Protein.

Physiopathology from The Alzheimer's Disease

Histopathological the AD is characterized by the formation and deposit of extracellular senile plaques, constituted of insoluble fragments of beta-amyloid peptide (Aβ) and of neurofibrillary intracellular tangles of the TAU protein hyper phosphorylated, followed by the significant loss of cholinergic neurons and neurotransmitters, just like the inflammatory process on the neuronal tissue. The loss of the balance between kinases and phosphatases substantially contribute to the aggregation of the TAU protein, just like post-translational modifications affect this balance. Oxidative stress, cleavage, glycation, nitration and polyamidation contribute to the formation of the neurofibrillary plaques. The main neurotransmitter evolved is the Acetylcholine (ACh), and its deficiency. The cholinergic hypothesis bases itself in the purpose of inhibiting the activities of the Acetylcholinesterase (AChE, enzyme responsible for the cleavage of ACh), increasing the levels of this neurotransmitter. The disease can evolve in three symptomatic manners: firstly, lapses of memory, after, the patient can present hallucinations and violent behave, and lastly total dependence on familiars, becoming uncapable of realizing essential activities like feeding and dressing yourself [6,7]. The (Figure 2) shows the stages of the disease's evolution.

1.	Dominant and non-dominant forms of Alzheimer's disease.
2.	Mutations of amyloid beta genes
3.	Relative increase in amyloid production throughout life
4.	Oligomerization after beta amyloid accumulation
5.	Effects of oligomerization on synapse efficacy
6.	Formation of diffuse plaques
7.	Alteration of the activity of kinases and phosphatases
8.	Generalized synaptic and neuronal dysfunction and neuronal loss with generalized neurotransmitter deficits
• **Dementia**	
Source: Adapted from SELKOE and HARDY, 2016.	

Figure 2: stages of the Alzheimer's disease evolution [8].

The Apolipo protein E (ApoE) is one of the main proteins that takes part in the human plasma, and from the lipoproteins of very low density (VLDL) and High Density (HDL), being involved so in the absorption, transport and redistribution of triglycerides and cholesterol by the tissues. It is also responsible for the damages reparation to the neurons. The ApoE is present in brain amyloid plaques, promoting the fibrinogenesis of the b-amyloid peptide and connecting itself to the TAU protein, decreasing its phosphorylation. There are some variables and/or mutations of the E4 gene (found in the 21 chromosome) that codifies this protein correlating the cholesterol with the AD. Patients with this dementia have significant elevated levels from the ApoE gene, increasing the affinity of this protein and the b-amyloid, facilitating like that its deposit and accumulate. The presence of the two alleles of this type of variation can decrease the instauration of the disease. The most recent technique, besides extremely sensitive to detection and quantification of the TAU protein in the plasma is called digital Elisa of unique molecule [9].

Actual Pharmacologic Treatment

The drugs most used to increase the life quality and retard the evolution from the disease are the inhibitors of the Acetylcholinesterase (AChE), Butyrylcholinesterase (BuChE) and the memantine, an antagonist of the glutamate receptors. The anticholinergics (IChE) are the most used, aiming to increase the concentration of the acetylcholine through the inhibition of the catalytic enzymes acetylcholinesterase and Butyrylcholinesterase. They are represented by the drugs: Galantamine, Donepezil and Rivastigmine. The Galantamine and Donepezil reversely inhibit

the Acetylcholinesterase, being of intermediary and long action, respectively, which possibilities a unique diary use, facilitating the treatment accession. However, the use the via of the P-450 cytochrome, which can cause some types of drug interactions. On the other hand, the Rivastigmine inhibit also the Butyrylcholinesterase and acts slowly and reversely (pseudo-reversely), its action is intermediary, but it has an active metabolite, that causes long lasting effects, it is the only drug in this indication eliminated by renal via, excluding the risks of hepatotoxicity.

Its administration facility by transdermal via (in a sticker way) it is also its differential [10]. In general, studies have shown that the use of Rivastigmine has been beneficial for patients with AD. The memantine is non-competitive antagonist of the NMDA type glutamate receptor. The glutamate is an excitatory neurotransmitter, but, if in high levels for a prolongated time, it is related to the neuronal death. Normally the memantine is used in association to the IChE, with low or none drug interaction, due also to the fact that its elimination is by renal via. It must be the initial treatment chosen in cases that the diagnoses are made in an advanced level of the disease [11,12].

Drug/ pharmacological treatment	Adverse reactions
Galantamine	Cholinergic effects, nausea, vomit, diarrhea, anorexia, dyspepsia, abdominal pain, increase of the acid secretion, blood pressure oscillation, arrhythmia, bradycardia, dizziness, headache, agitation, insomnia, cramps, sweating, increase of the bronchial secretion.
Donepezil	Cholinergic effects, nausea, vomit, diarrhea, anorexia, dyspepsia, abdominal pain, increase of the acid secretion, blood pressure oscillation, arrhythmia, bradycardia, dizziness, headache, agitation, insomnia, cramps, sweating, increase of the bronchial secretion.
Rivastigmine	High level cholinergic effects, nausea, vomit, diarrhea, gastrointestinal effects, weight gain, dyspepsia, abdominal pain, increase of the acid secretion, blood pressure oscillation, arrhythmia, bradycardia, dizziness, headache, agitation, insomnia, cramps, sweating, increase of the bronchial secretion.
Memantine	Diarrhea, vertigos, headache, insomnia, agitation, excitation and tiredness.
Source: By the author.	

Immunotherapy

The beta-amyloid protein suffers the beta-secretase and alfa-secretase enzymes action. The oligomers, monomers and beta-amyloid peptides (isoforms) surge from this cleavage. The most common of these is the Aβ40 (beta-amyloid peptide with 40 amino acids), could appearing also some of the type Aβ42 (beta-amyloid peptide with 42 amino acids), this with tendency to agglomeration and super produced in the AD. They are eliminated by brain enzymes, occurring its debug, however, if its elimination is smaller than its production, it can happen the formation of insoluble neurotoxic tangles, this being known as the amyloidogenic via. In the last year's drugs have been developed aiming the elimination and the aggregation of the bets-amyloid, acting through the inhibition of this enzymes and the stimulation of the immune system to produce anti bodies [13,14].

Active Immunization

In the active immunization an antigen capable to induce antibodies mediated by an immunization response through the vaccine is administrated. With few administrations is possible to obtain a long-lasting reaction anti body, however, in very old people it may not be sufficient. The first created was the AN-1792, peptide administration Aβ42 made synthetically and producing anti bodies that stimulate the debug of the beta-amyloid protein, however the studies were closed after 12 months, in January of 2002, due to the adverse effects and the occurrence of meningoencephalitis cases. In addition, even with the shutting of the researches, it was found in autopsies that were a significative reduction on the quantities of the senile plaques. After the synthesis of the AN-1792 new molecules were developed with bigger selectivity just like the ACC-001, that also had its studies shut in 2014 due to adverse effects, including the pectoris angina a strong autoimmune reaction. Another substance in studies is the CAD-106 (Novartis), in the III level of clinical research, recruiting participants to investigate the protease beta-secretase, an aspartyl inhibitor and its individual synthons with the vaccine utilization [15-17].

The Aadvac 1 (Axon Neuroscience SE) is the first vaccine that is nowadays in test level III. It is composed of synthetic peptide derived of the tau protein, that acts against the tau protein in the non-active or short form (which is more susceptible to the aggregation), being tested in patients in moderated disease stage. The vaccine stimulates a very fast immune reaction associated to the production of polyclonal Anti-Tau phosphorylated anti-bodies, that are capable of passing through the Blood Brain Barrier (BBB) and being absorbed by the neurons through low affinity receptors to after binding with pathologic tau proteins inside the lysosomal system. The vaccine differs in a selective way the pathologic tau and the physiologic tau, connecting itself only to the pathologic forms. Studies suggest that this vaccine can also be effective if used in advanced stages of the AD [18,19].

It is important to say that there is a phenomenon called immune senescence that consists in a reduced immunogenicity, caused by the low quantity of Th cellules (responsible for the maximization of the B cellules anti-bodies secretion), due to a certain type of auto-tolerance observed in older people in the face of the vaccination, which can cause low reaction levels. In the other hand, this phenomenon only occurs in AD patients that have elevated numbers of the anti-aβ anti-bodies that eliminate amyloid plaques, although the oligomeric soluble forms of anti-bodies are not reduced and the progressive neurodegeneration is not avoided [20].

Passive Immunization

The passive immunization consists in the direct administration of monoclonal anti-bodies. The tau protein has cis and trans spatial conformations, that can change its stability. The cis position seems more pathological/ propitious/ resistant to the disaggregation, in the other hand, the trans position seems more likely to have normal functions, instead of being pathological, what make relevant the question of a possible selectivity/specificity to the anti-bodies used for its anti-aggregation. This selectivity can be given by the recognizing of a methylene group in the cis position [21,22].

The Aducanumab (Biogen), the Bapineuzumab (Pfizer) and the Labetuzumab (Lilly) are monoclonal anti-bodies in the III tests level, with exception from the Bapineuzumab, that was discontinued on this level for not presenting any effective and presenting diverse side effects. All of them have affinity and capacity to connect with the soluble or fibrillar form of the beta-amyloid protein. They induce the Th cellules to produce strong reactions, that, as above said, are responsible for the maximization of the B cellules anti-bodies secretion. The studies suggest that these should be used in initial stages from the AD, in order to obtain less neuronal losses, due to the fact, also seen above that is the immune senescence phenomenon (low Th cellules values in very old people). There exist some ways of level mensuration and verification of the quantity of the beta anti-bodies, just like immunochemistry, Western Blot, Elisa, Elisa competitive and plasma surface resonance. A way to potentialize the mentioned effect of the anti-bodies is to figure out a method for those to penetrate in the brain [19,20,23]. The (Table 2) shows the new treatments for the Alzheimer's disease.

Drug/ Manufacturer	Study Level	Action Mechanism
CAD-106 (Novartis®)	3	Stimulate debug of the beta-amyloid protein.
Aadvac1 (Axon Neuroscience®)	3	Synthetic peptide derived from the Tau protein, that connects and signalizes the pathologic Tau.
Aducanumab (Biogen®)	3	Monoclonal anti-body, connects with the soluble or fibrillar beta-amyloid protein.
Solanezumab (Lilly®)	3	Monoclonal anti-body, connects with the soluble or fibrillar beta-amyloid protein.
Source: The very author.		

Table 2: New treatments for the Alzheimer's disease [15-20,24].

Discussion

The strategies based on the cholinergic hypothesis are being replaced for the research of new therapeutic alternatives based on the tau protein hyper phosphorylation and the beta-amyloid peptide accumulate.

Two negative factors to be considered about the vaccination for the AD treatment are the necessity of a long time of drug administration with frequent vaccinations so that there will be a massive production of anti-bodies and immunity; and the necessity of the immunization only being effective with the immunocompetent individual, which is a worry situation when discussing elder people. In order to solve this problem, studies constantly analyze the used adjuvants on these, for some of them produce synergic effects and the other produce antagonist effects [22].

In the other hand, a positive factor about the vaccination is the possibility of this one generates a strong immune reaction, with high anti-bodies affinity, beyond being very safe, without toxic effects or cardiotoxicity, for example. The positive factor about the monoclonal nti-bodies is the significant reduction on the insoluble phosphorylated tau protein levels [23].

Conclusion

Treating the Alzheimer's Disease is a hard job, once that, as above mentioned, this disease has no cure and bring countless losses to the patient, culminating in death. The drugs already used only extend the lifetime of the patient, but they cannot retard the cognitive losses very much with the pass of the time and the disease evolution. However, the new treatments developed from the immunotherapy promise to decrease the hyper phosphorylated tau protein accumulate and the beta-amyloid protein, decreasing like that the cognitive losses, and bringing good hope and even a possible bure in the future to this disease. Taking precipitated conclusions would not be possible, once the biggest part of the new immunotherapies is in tests level, waiting for the approval so that they can be used. By now, we supper our expectative with the good results, and with until this can be approved and used as soon enough.

Conflicts of Interest

There is no conflict of interest involved in this publication.

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