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8. Strategies against β-amyloid protein as therapeutics in Alzheimer's disease

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Abstract. Alzheimer's disease (AD) is the main neurodegenerative disorder, causing total intellectual disability in patients suffering from it. It is considered an important public health problem of the 21st century due to its high global prevalence and socioeconomic impact. The amyloid hypothesis of AD proposes that β-amyloid peptide plays a key role in this disease. Several pharmacological strategies have been developed

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with the aim of inhibiting the formation of β-amyloid peptides, such as β-secretase and γ-secretase inhibitors. Other anti-amyloid treatments include passive and active immunotherapies focused on inhibiting β-amyloid peptide aggregation. However, the most recent phase 3 clinical trials of solanezumab, a humanized monoclonal antibody that promotes the clearance of β-amyloid in the brain, show no efficacy of this antibody in patients with mild AD, suggesting that the amyloid hypothesis of AD should be revised. In this manuscript, the current and ongoing treatments acting primarily on the β-amyloid protein are reviewed.

Introduction

Alzheimer's disease (AD) is the most frequent progressive neurodegenerative disorder that causes dementia among the world's population over 65 years (between 50 and 70% of the cases of dementia) [1]. The disease is chronic and progressive, causing deficits of multiple brain functions (mainly at the cortex and hippocampus levels) including memory, thinking, orientation, comprehension, calculation, learning ability and language [2].

Despite the great scientific and clinical advances in AD in the last 30 years, the treatments currently available are only symptomatic; thus meaning that they alleviate the symptoms of the disease by acting at different levels of the neuropathological process [2]. Although they improve the life quality of the patients, none can actually cure or delay the rapid and fatal progression of the disease.

Nowadays, there are only four drugs on the market approved for the treatment of AD. These drugs can be divided in two groups: acetylcholinesterase inhibitors (AChEI) and N-methyl-D-aspartic acid receptor (NMDAR) antagonists. AChEI includes donepezil, rivastigmine and galantamine [2, 4]. The mechanism of action of AChEI is to increase cholinergic transmission by inhibiting acetylcholinesterase in the synaptic cleft and therefore they may slightly increase the cognitive ability of patients with AD. Since in AD the levels of the neurotransmitter glutamate are pathologically elevated, memantine (MEM) is an NMDAR receptor antagonist that reduces excitotoxicity by blocking this ionotropic receptor. Both groups of drugs are indicated for the treatment of patients with moderate or severe AD [3,4]. However, it has been shown that none of these drugs actually represents a cure for the disease, since its effects are only palliative and its efficacy decrease with time.

Notwithstanding, new treatments and therapeutic strategies are being investigated in order to delay the course of the disease. These are mainly

directed to the neuropathological complexity of AD, encompassing multiple targets and are intended to be administered in the early stages of AD.

For future treatments to be effective, it will be necessary to develop new diagnostic techniques that allow an earlier diagnosis of AD in a pre-clinical phase (before symptoms appear), or even to predict the development of the disease.

The prevention of AD is a realistic challenge for researchers, but to make it possible it is necessary a better understanding of the aetiology and the extent to which environmental factors and lifestyle influence the risk of developing the disease.

1. Alzheimer's disease: Hypotheses

The cause or causes that promote the development of AD are still unknown. However, different hypotheses (Fig. 1) have been proposed thus contributing to understand the complex neurodegenerative process of this disease [5-8]. Most experts agree that it develops as a result of a combination of multiple modifiable and non-modifiable risk factors (age, sex, family history and genetics, environmental and lifestyle) rather than a single cause [9-11].

The two proposed etiological hypotheses most accepted by the scientific community currently are:

1. The hypothesis of the amyloid cascade, which suggests that the neurodegenerative process observed in the brains of patients with AD would be mainly due to the cytotoxic events triggered by the formation, aggregation and deposition of β-amyloid peptides [6,9]. This hypothesis has been strongly supported by researchers because of the genetic findings in molecular biology studies, opening new lines in the search for drugs for the treatment of AD, such as inhibitors of β and γ-secretase or enhancers of α-secretase [4]. According to this hypothesis, the initiation of AD would be triggered by the following process: APP (amyloid precursor protein) would be metabolized by the amyloidogenic route, which would cause an excess in the production of the β-amyloid peptide (βA) and / or a defect of its elimination [4,5].
2. Tau phosphorylation hypothesis. βA protein is obtained from the catabolism of APP, a membrane protein with a single domain (an intracellular and extracellular part) found in different cell types,

including neurons, glial cells, astrocytes and oligodendrocytes, [7,8]. It is encoded by a gene located on chromosome 21 which, when expressed, gives rise to 8 isoforms, with APP695 being the most abundant in the brain. This protein is cleaved by α-, β-, and γ-secretase enzymes and a complex of proteins containing the presenilin gene (PSEN1). In a physiological situation, following the non-amyloidogenic pathway, APP is catabolized by α-secretase, producing an APPα fragment (s) which remains in the extracellular space, and an 83-amino acid carboxy-terminal fragment (C83). APPα regulates neuronal excitability, improves synaptic plasticity, learning, memory and increases the resistance of neurons to oxidative and metabolic stress [5-8]. However, in a neuropathological situation, APP is metabolized by the amyloidogenic pathway, in which BACE1 (β-secretase 1) cleaves APP by the N-terminal end and the γ-secretase cleaves the C-terminal end, obtaining the fragments Aβ40 / 42, which remain in the extracellular space, and a C-terminal fragment of 99 amino acids (C99), which can be transported into the cell and translocated to the nucleus, where it could induce expression of genes that promote neuronal death by apoptosis [6,7]. APP regulates neuronal survival, protection against toxic external stimuli, neurite outgrowth, synaptic plasticity and cell adhesion. Notwithstanding, when it is transformed into βA 40/42 peptides, it interferes with synapses, decreases neuronal plasticity, alters the energy metabolism and glucose, induces oxidative stress and mitochondrial dysfunction, and disrupts cellular calcium homeostasis [7]. Differential cleavage by β-secretase produces different βA peptides: βA40 is the predominant species, whereas βA42 is the major component of senile plaques. The peptide βA42 is more prone to aggregation and more neurotoxic than βA40. According to this, it has been proposed that βA is the pathogenic species in AD. In this way, βA42 is oligomerized and accumulated as senile plaques in the brain, thus exerting toxic effects on neuronal synapses. In a second stage, there would be a glial response, activation of the astrocytes and the surrounding microglia, which would release cytokines or components of the complement system leading to inflammatory responses. Likewise, oxidative stress is established in the neuron and there is an

alteration in calcium ion homeostasis, which causes hyperactivation of protein kinases and the inactivation of phosphatases. For this reason, the tau protein is hyperphosphorylated and forms the neurofibrillary tangles, which accumulate in the synapses and in the neuronal bodies causing neuronal death by apoptosis and a deficiency of neurotransmitters. All this cascade of processes ends in instituting dementia [7].

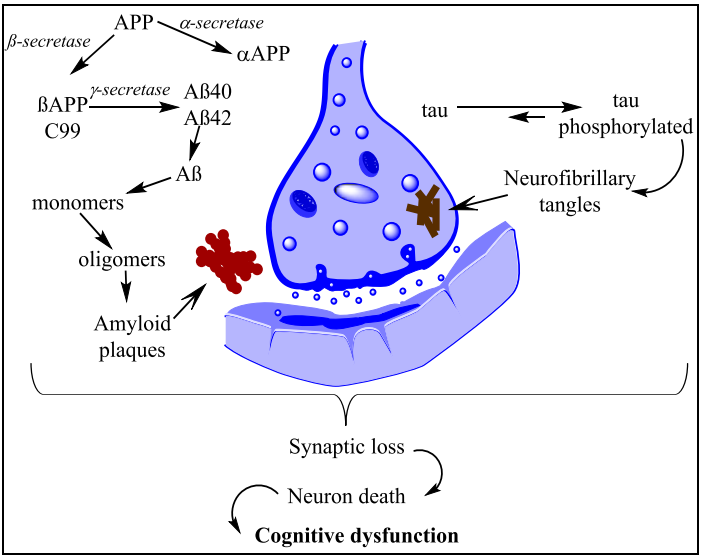

Figure 1. Alzheimer's disease hallmarks and its process.

Thus, both βA (mainly βA42) and tau proteins have been the main targets for modifying therapies of AD [4]. From this point of view, AD could be prevented or treated effectively by the decrease in the production of βA42 and the phosphorylation of the tau protein, in addition to the prevention of the aggregation or poor folding of these proteins, thus neutralizing or eliminating the toxic aggregated or poorly folded forms of these proteins, or a combination of these modalities [4-9].

Likewise, alternative hypotheses such as the alteration of mitochondrial activity, the neuroinflammatory hypothesis, the metabolic hypothesis (namely cholesterol and insulin), and the dendritic hypothesis have been also proposed [10-15]. All these lines of thought confirm the

complexity of this disease, in addition to the fact that the mechanism of neuronal death by apoptosis is not yet known at all.

2. Therapeutic strategies for the development of drugs to modify the course of Alzheimer's disease

Given the expected increase in the number of cases of AD patients in the coming decades, it is necessary to develop more effective treatments capable of modifying the course of the disease.

During the last decade, from 1998 to 2011, about 100 compounds have been evaluated with the objective of modifying the course of AD. Unfortunately, they have failed in the clinical development phase [1,3]. The reason for this failure could be explained, as already mentioned, by the multifactorial aetiology and pathophysiological complexity of the disease. Finding a suitable and effective drug in the whole population tested is a very complicated task.

Although some key aspects of the pathogenesis of AD remain to be solved, the scientific advances of the last 25 years have allowed to reasonably establishing several strategies for the development of treatments with potential to modify the course of this disease. Thus, among the different therapeutic strategies that are being investigated, those aimed at reducing the formation of βA42 and the phosphorylation of the tau protein are the most important [3]. These two types of injuries are the ones that have provided the greatest advances in the field, and could be the key to the treatment of AD in the near future.

Following the amyloid hypothesis of AD, huge efforts have been made with the aim of developing effective drugs in the treatment of AD [4, 6]. However, the multiple clinical failures of the compounds in development have led researchers to question this hypothesis. Notwithstanding, new compounds are being investigated, along with new diagnostic tools for AD. This is important, since the reason for these failures could be the lack of suitable biomarkers that would allow recruitment of patients in clinical trials before they reach a very advanced phase of the disease, in which any therapeutic intervention is useless [1].

The different anti-amyloid strategies are designed to act at different points in the metabolism of APP such as decreasing production of βA peptides. In the attempt to decrease the production of βA, the current research has focused on the modulation of the enzymatic pathways

responsible for the abnormal processing of APP, i.e. inhibition of γ and / or β-secretase and α-secretase activation.

2.1. Inhibitors of β-secretase (BACE1)

The enzyme β-secretase is responsible for initiating the amyloidogenic processing pathway of APP [7]. The development of inhibitors of this enzyme is quite challenging because, in addition to APP, β-secretase has many more substrates, among which we find neuregulin-1, involved in the myelination of the peripheral nerves [16-18]. This fact makes the non-specific inhibition of the enzyme susceptible of causing adverse effects [16]. The structure of the enzyme is another main problem. Since it belongs to the class of aspartyl proteases, the inhibitor must be a large hydrophilic molecule, which makes it difficult to cross the blood-brain barrier [19]. Currently, several compounds are being investigated to overcome these obstacles and to make some of them effective in the treatment of AD [19]. Recent studies indicate that two inhibitors of β-secretase, E2609 and MK-8931, are extremely effective in reducing the production of βA levels up to 80-90% in cerebrospinal fluid (CSF) in humans [17-19].

2.2. Inhibitors and modulators of γ-secretase

The γ-secretase enzyme is responsible for the final phase of APP processing by the amyloidogenic pathway, resulting in βA40 and βA42 peptides. Although its inhibition was a promising advance for the modification of the disease back in 2001, showing for the first time an in vivo decrease in the production of βA, the development of γ-secretase inhibitors shows similar problems to those of β-secretase inhibitors [19-21].

In addition to APP, γ-secretase processes multiple proteins, including the Notch protein, responsible for regulating cell proliferation, development, differentiation, communication, and cellular survival status [20,21]. For this reason, nonspecific inhibition of the enzyme results in serious adverse effects, leading to severe limitations in clinical trials.

Semagacestat (LY450139) is an example of this therapeutic group. As a functional γ-secretase inhibitor, it was shown to decrease βA levels in blood and cerebrospinal fluid in humans [22]. However, the results of this and other similar studies (NCT00762411; NCT01035138; NCT00762411)

showed that semagacestat did not decrease the slow progression of the disease and, in addition, its administration was associated with worsening cognition. Another example is avagacestat (NCT00810147; NCT00890890; NCT00810147; NCT01079819), whose pharmacokinetics and effectiveness have been evaluated in several clinical trials in AD patients [23-25].

To avoid the adverse effects derived from these γ-secretase inhibitors, the use of γ-secretase selective modulators (MSGS), which block the enzyme by altering the processing of APP without interfering with the signalling of other ways such as Notch, has been proposed [21]. The development of MSGS began with the observation that several anti-inflammatory drugs (NSAIDs) decreased βA42 peptide levels in human H4 neuroglioma cells as well as transgenic mice [26,27]. Examples of these drugs are ibuprofen, sulindac, indomethacin, and flurbiprofen. (*R*)-Flurbiprofen (tarenflurbil) inhibits cyclooxigenase-1 to a low extent, and it was tested in a clinical phase III study for the treatment of AD. However, both tarenflurbil and ibuprofen failed in their respective clinical trials [27,28].

CHF5074 is a non-steroidal anti-inflammatory derivative devoid of cyclooxygenase inhibitory activity [29]. In vitro, CHF5074 behaves as a β-secretase modulator, preferentially by inhibiting the production of βA42 [30,31]. As we have already mentioned, the long-term use of NSAIDs confers some protection against AD, which led to the widespread study of NSAIDs against the production of βA42. However, negative results observed in NSAID clinical trials suggest that protection against AD is not a general benefit provided by all these drugs.

An example of these MSGS is NIC5-15, a molecule of natural origin. Specifically, NIC5-15 is pinitol, a natural cyclic sugar alcohol [32]. Interestingly, pinitol also acts as an insulin sensitizer. This compound modulates β-secretase and reduces the production of βA without affecting the cleavage of the Notch-β-secretase substrate [32,33]. It has been suggested that the compound improves function deficit and memory in preclinical models of AD neuropathology [33]. Studies in animals and human trials have shown that NIC5-15 is safe and also acts as a sensitizer for insulin actions [32]. In preclinical studies, at doses higher than those previously studied in clinical trials, NIC5-15 was found to interfere with βA accumulation. This data suggest that NIC5-15 may be a suitable therapeutic agent for the treatment of AD mainly for three reasons: it is a

secretory inhibitor preserving Notch and, in addition, it is potentially an insulin sensitizer and is being investigated as an inhibitor of the inflammatory process particularly inhibiting the activation of microglia.

2.3. Activation of α-secretase

Activation of the α-secretase enzyme leads to the processing of APP by the non-amyloidogenic pathway, thereby decreasing the amount of APP available for the amyloidogenic pathway. The result is the formation of a soluble βA, which has been shown to play a neuroprotective and synaptogenic stimulatory role.

Thus, the activation of α-secretase is an attractive strategy for the development of disease modifying drugs. Different compounds related with the non-amyloidogenic pathway have been investigated, such as agonists of muscarinic acetylcholine receptors, glutamatergic receptors, serotoninergic receptors, and activators of protein kinase C (PKC). However, not many compounds have been found that effectively modulate this pathway in animal models, so not many of these compounds can be found in clinical trials.

Epigallocatechin gallate (EGCG) is a polyphenolic flavonoid extracted from green tea leaves and it is considered its key bioactive ingredient. It has been reported to have beneficial clinical effects ranging from anti-tumour, anti-inflammatory and neuroprotective action, and it may also have a beneficial effect on cognitive function [34]. It has been proposed that EGCG inhibits the formation of toxic βA oligomers, in addition to activating α-secretase. A clinical trial (NCT00951834) is currently being conducted to evaluate the efficacy of EGCG in early stages of AD.

Briostatin 1 is a modulator of PKC which also seems to have immunomodulatory effects. There is preclinical data showing that this compound increases cognitive ability [35].

Etazolate (EHT0202) stimulates the neurotrophic action of α-secretase and also inhibits neuronal death induced by βA, thus providing symptomatic relief and further modifying disease progression. In a recent phase IIa clinical study in 159 patients with mild to moderate AD, EHT0202 has been shown to be safe and generally well tolerated [36]. These early encouraging results further support the development of EHT0202 to assess its clinical efficacy and confirm its tolerability in a large cohort of patients with AD in a longer period of time [36].

Moreover, acitretin is a retinoid that acts as a retinoic acid receptor agonist. It is primarily used to treat severe psoriasis [37]. In preclinical models, it increases the expression of ADAM-10, an α-secretase of the human amyloid precursor protein (APP) [37-39]. Acitretin has been reported to activate the non-amyloidogenic pathway of APP in neuroblastoma cells and to reduce βA levels in APP / PS1 transgenic mice. [37-39].

2.4. Amyloid antiaggregants

The extensive evidence on the neurotoxic and synaptotoxic activity of amyloid aggregates, constitute the scientific basis for the development of inhibitors of the aggregation of βA peptides.

The only inhibitor of βA aggregation to reach phase III is the 3-amino acid synthetic 1-propanesulfonic acid (3APS, Alzhemed, tramiprosate) [40,41]. This drug was designed to interfere with or antagonize the interaction of βA with endogenous glycosaminoglycans. Glycosaminoglycans have been shown to promote βA aggregation by interfering with the formation of amyloid fibrils and by stabilizing plaque deposition [41]. However, the disappointing results of the phase III trial in 2007 led to the suspension of the European Phase III trial.

Colostrinin, a proline-rich polypeptide complex derived from ovine colostrum, inhibits βA aggregation and its neurotoxicity in cellular assays, and improves cognitive performance in preclinical animal models [42]. Although a Phase II trial showed slight improvements in the Mini Mental State assessment in patients with mild AD over a 15-month treatment period, this beneficial effect was not maintained for another 15 months of additional continuous treatment.

The compound called scyllo-inositol is capable of stabilizing the oligomeric aggregates of βA and inhibiting βA toxicity in the mouse hippocampus. An 18-month clinical trial in the search for dose, safety and efficacy of scyllo-inositol (ELND005) in mild to moderate AD patients was carried out. Three doses of ELND005 (250, 1000, and 2000 mg) were evaluated, being 250 mg the most adequate. Future long-term clinical studies should be performed to elucidate if there is enough evidence to support or rule out an ELND005 benefit in AD.

Several compounds with an antiaggregating effect, such as PBT1 (clioquinol) and PBT2, have been evaluated. Clioquinol was investigated as a treatment for AD since it blocks the interaction between metals and βA in the brain [45]. It has been proposed that increased levels of bioactive metals

in aging brain accelerate the formation of amyloid plaques, as well as neurotoxic oxidative processes. The fundamental reason for the evaluation of clioquinol was that it would prevent accumulation of βA and, in addition, restore homeostasis of cellular levels of ions such as copper and zinc. Unfortunately, these compounds failed during clinical trial phases II and III due to lack of efficacy.

2.5. Compounds favouring the elimination of amyloid aggregates and deposits

Another amyloid-directed strategy is based on promoting the clearance of aggregates and amyloid deposits. To achieve this, three different strategies have been evaluated:

1) Activation of enzymes responsible for degrading amyloid plaques

   Amyloid aggregates and plaques are degraded by different proteases, including neprilysin, insulin degrading enzyme (IDE), plasmin, endothelin-converting enzyme, angiotensin-converting enzyme, and metalloproteinases [9,46,47]. In AD, the levels of these enzymes decrease, thus contributing to the formation and accumulation of amyloid plaques [46]. Despite being an attractive anti-amyloid strategy for the development of disease-modifying drugs, no protease activator has been evaluated so far due to the lack of specificity of these compounds.

2) Modulation of βA transport from the brain to the peripheral circulation

   The transport of βA between the central nervous system (CNS) and the peripheral circulation is regulated by; 1) apolipoproteins, with APOEε4 promoting the passage of βA from the blood to the brain; 2) low density lipoprotein receptor (LRP)-related protein, which increases the outflow of βA from the brain into the blood and; 3) the receptor for advanced glycation end products (RAGE), which facilitates βA entry into the CNS [48-51].

   Although different strategies -like peripheral LRP administration- have been proposed to increase βA transport from the brain to the peripheral circulation, only compounds aimed at inhibiting / modulating RAGE have reached clinical development. These include PF-0449470052, which failed in the Phase II clinical trial, and TTP4000, currently in Phase I clinical trials (NCT01548430). The study ended in February 2013, and no results have been published so far.

3) Specific anti-amyloid immunotherapy

This is the most studied strategy with the aim of reducing amyloid burden in AD. There are two types of anti-amyloid immunotherapy:

a) Active immunotherapy: Active immunization (vaccination) with either βA42 (the predominant form of βA in the amyloid plaques of AD) or other synthetic fragments has been successfully evaluated in transgenic AD mouse models. The assays are generally based on the stimulation of T-cells, B-cells, and the immune response by activating the phagocytic capacity of the microglia. The results of the initially promising trials have been partially suspended due to the appearance of meningoencephalitis in some patients. When the first vaccine (AN1792, consisting of 42 amino acid peptide) was tested on patients, it was found to give rise to neurological inflammatory processes, such as aseptic meningoencephalitis, as a result of an anti-AN1792 autoimmune response. These adverse effects forced the discontinuation of Phase II clinical trials [53].

In order to avoid the non-specific immune response derived from immunization with complete βA (Aβ42) peptides, a second generation of vaccines has been designed by using shorter segments of βA (Aβ1-6) peptide, which favored a humoral response to a cellular immune response. CAD 106, designed by Novartis, was the first second generation vaccine that reached the clinical stages of development [54]. It has recently completed Phase II clinical trials, where a specific response of βA antibodies was observed in 75% of the patients tested, without giving rise to inflammatory adverse responses. ACC-001 has recently completed some Phase II trials (NCT01284387 and NCT00479557). Although there is another Phase II trial in process (NCT01227564), the pharmaceutical company has declined to continue the investigation. There are currently other vaccines in preclinical stages of development, such as the peptide ACI-24, βA1-15 tetra-palmitoylate reconstituted in a liposome, MER5101 and AF205 [55-57].

b) Passive immunization: It consists of passive -intravenous- administration of monoclonal or polyclonal antibodies directed against βA in the patient. Thus, an anti-βA immune response is achieved without the need for a pro-inflammatory reaction mediated by T cells [57]. Transgenic animal studies have demonstrated that passive immunization, in addition to reducing neuronal amyloid burden, improves cognitive deficits even before

the elimination of neuronal amyloid plaques [58]. This could be attributed to the neutralization of soluble amyloid oligomers, which are increasingly believed to play a fundamental role in the pathophysiological cascade of AD [57,58].

Bapineuzumab and solanezumab, the two monoclonal antibodies that have reached the most advanced stages of clinical development, failed in 2012 in two phase III clinical trials as they did not show the expected benefits in patients with mild-moderate AD. Bapineuzumab is a humanized monoclonal antibody against the N-terminal end of βA (Aβ1-5), while solanezumab is a humanized monoclonal antibody designed to bind to the central portion of βA (Aβ12-28) [59,60]. It is noteworthy that, despite the reduction of key AD biomarkers, such as amyloid brain plaques and phosphorylated tau protein in the cerebrospinal fluid, bapineuzumab failed to produce significant cognitive improvements in two clinical trials [61,62].

New phase III clinical trials with solanezumab are currently underway (NCT01127633 and NCT01900665), assessing its efficacy and safety in patients with mild AD (NCT02051608), with prodromal AD (NCT01224106), and in elderly asymptomatic population at high risk of losing memory (NCT02008357) [62]. Another monoclonal antibody, gantenerumab, is being tested with the aim of evaluating its modifying potential in people at risk of developing AD due to an autosomal dominant mutation of the DIAN-TI gene (NCT01760005) [63,64]. Gantenerumab is a fully human IgG1 antibody designed to bind with high affinity to a conformational epitope on βA fibers [63,64]. The therapeutic basis for this antibody is that it acts by degrading the amyloid plaques by a process of recruitment of the microglia and activation of phagocytosis. Experimental studies in transgenic mice support this hypothesis [65]. In parallel, a number of phase III clinical trials evaluating gantenerumab are being performed.

Specifically, in a phase III clinical trial, infusions of 400 mg of solanezumab or placebo once a month for 80 weeks were administered to patients with mild to moderate AD. The results seem to indicate a tendency to improve cognition with solanezumab in people with mild AD, but it does not appear to be statistically significant. Thus, we should be cautious and wait for more results.

Crenezumab (MABT5102A), is another humanized monoclonal antibody in phases of clinical development [66]. In April 2014, a phase II

clinical trial was completed to evaluate its efficacy and safety in patients with mild-moderate AD (NCT01343966), although the results are not yet available. Currently, two phase II trials with crenezumab are underway. The most recent began in 2013 in order to evaluate their efficacy and safety in asymptomatic patients with the autosomal dominant PSEN1 mutation (NCT01998841).

Other monoclonal antibodies against βA developed so far include PF-04360365 (ponezumab), which targets the free C-terminal of βA (specifically βA34-41); MABT5102A, which binds to monomers, oligomers, βA and fibrils with equally high affinity; and GSK933776A, which, similarly to bapineuzumab, targets the N-terminal sequence of βA [66]. In addition, other passive immunotherapies, such as those assessing GSK933776A, NI-101, SAR-228810 and BAN-2401 are being developed, most of which are in Phase I clinical trials.

Finally, gammagard™ is an antibody preparation from human plasma. Concerning this preparation, a safety record for human use has been established for certain autoimmune conditions. Gammagard ™ has also been evaluated for the treatment of AD in a small number of patients (NCT00818662). These intravenous immunoglobulin mixtures contain a small fraction of polyclonal antibodies directed against the βA peptide, which is believed to counterbalance the synaptic toxicity caused by βA [67-69]. In addition, this intravenous IgG immunoglobulin has immunomodulatory effects, besides favoring the phagocytosis of the microglia [69].

3. Conclusion

Several attempts have been made to treat AD by reducing cerebral βA levels. Overall results obtained so far suggest that anti-amyloid drugs, as a specific group, could have a detrimental effect on the symptoms of the disease. On the other hand, the investigators argued in favor of carefully differentiating between these therapeutic approaches according to the underlying mechanism, rather than grouping them all together as anti-amyloid treatments. In addition, alternative approaches have been proposed to explain the failure of the amyloid hypothesis. Specifically, the adaptive response hypothesis proposes that βA may accumulate by an adaptive response to chronic stress stimuli in the brain [9]. According to this, stress stimuli are the pathogenic triggering signals/pathways of the late onset of AD and, therefore, would be suitable candidates for

therapeutic intervention in the disease. Such stimuli would include oxidative stress, metabolic dysregulation (cholesterol homeostasis, insulin resistance, etc.), genetic factors, and inflammatory response. Each of these stimuli is capable of eliciting a response in which more βA would be generated, and the nature of this response would determine the clinical progression of AD. Following this line of thought, acting on these stress stimuli could be an adequate pharmacological treatment to curb AD. Accordingly, intranasal insulin is recently being evaluated as a promising strategy for the treatment of AD. Positive results could confirm that βA is not the only noxious agent responsible for AD.

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