

Amyloid- β Immunotherapy on Alzheimer disease: Prevention and Therapeutic Target

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ABSTRACT

Alzheimer disease (AD) is the most common neurodegenerative disease and form of dementia. The peptide amyloid- β ($A\beta$) is a most therapeutic target in AD on the basis of pathological and genetic suffices that supports a role for this molecule in the disease process. Studies show that $A\beta$ immunotherapies (Active and passive) have been revealed to alleviate cerebral $A\beta$ levels and improve cognition in animal models of AD. In humans, clinical trial phase 2 AN1792 conducted by Elan et al stated that $A\beta$ vaccine was stopped when ~6% of the immunized patients developed meningoencephalitis. However, some plaque clearance and modest clinical improvements were observed in patients following immunization. In this study, $A\beta$ immunotherapies will be discussed. Passive and active method of treatment in human and non-human primate with AD will also be review. Preclinical studies and the limited data from clinical trials and non-human primates' evidence suggest $A\beta$ immunotherapy as the most effective in preventing or slowing the progression of AD when patients are immunized before or in the very earliest stages of disease onset. AD Biomarkers and imaging technology have improved greatly over the past 11 years and, in the future, can be used to identify pre-symptomatic, at-risk individuals who might benefit from $A\beta$ immunotherapy.

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Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease that affects more than 18 million elderly people worldwide. Its prevalence increases with aging, affecting 8–11% of individuals over age 63, and about 42% of persons over 80 years of age. AD is characterized by cognitive dysfunction, memory loss, behavior changes, impairments in the activities of daily living (ADL), incontinent and reduces the quality of life. Studies revealed the neuropathological hallmarks of AD are cerebral amyloid angiopathy and extracellular neuritic plaques formed by $A\beta$ deposits, and intracellular neurofibrillary tangles (NFT) composed of paired helical filaments of hyperphosphorylated protein tau, neuronal loss, neuritic dystrophy, inflammation and gliosis. The aetiology of AD are unknown, but accumulating studies supports the " $A\beta$ hypothesis", which characterized by insufficient clearance, overproduction or aggregation of $A\beta$ peptide results in neuronal loss and dysfunction underlying dementia in AD.

Evidence from Town. T et al shows that $A\beta$, a 39–42 residue peptide weighing ~ 4 KD, is formed through the "amyloidogenic pathway" in which amyloid precursor protein (APP) is sequentially cleaved by β - and γ -secretase as opposed to the constitutive non-amyloidogenic pathway that involves processing APP by α -secretase. Mutations in presenilin (PS) 1 and 2 genes can cause

onset forms of AD, providing genetic support for the role of $A\beta$ in AD. Researcher findings stated that Apolipoprotein E, especially its $\epsilon 4$ isoform, $\alpha 1$ -antichymotrypsin, and C1q complement factor can greatly increase the aggregation of $A\beta$. Town. T et al further stated that once $A\beta$ aggregates, its conformational change is thought to initiate a neurodegenerative cascade including impairment of long-term potentiation, changes in synaptic function, and accelerated formation of neurofibrillary tangles (NFT) that will ultimately lead to synaptic failure and neuronal death [1]. Thus, the $A\beta$ cascade has become a central therapeutic target and reducing the $A\beta$ burden in the brain by immunotherapy has developed as a promising strategy for the treatment of AD.

Passive and Active $A\beta$ Immunotherapy

Alzheimer disease (AD) treatments at present do little to modify the disease progression and also provide modest symptomatic benefit for some patients. Results from Humans from clinical trial and non-human primates, active and passive $A\beta$ immunotherapies have become potentially useful disease-modifying strategies for combating AD. Active immunization described administration of synthetic $A\beta$ peptide or $A\beta$ fragments conjugated to a carrier protein and adjuvant to stimulate cellular and humoral immune responses in the host that, in turn, result in the generation of anti- $A\beta$ antibodies. In passive immunotherapy, $A\beta$ -specific antibodies are directly injected into the body of the host, bypassing the need for engagement of the immune system. In both active and passive $A\beta$ immunotherapies, anti- $A\beta$ antibodies remove the $A\beta$ from brain.

Evidence of A β (Passive & Active) immunization in mice Evidence from Schenk et al reported the beneficial effect of A β immunotherapy in a preclinical study of A β ₁₋₄₂ active immunization in transgenic (PDAPP) mice. Immunizing mice prior to the onset of pathology reduced levels of cerebral amyloid and produced high serum antibody titers. Also, amyloid deposition was reduced in mice that were immunized after they had developed significant amyloid pathology. This work was later confirmed by active intranasal immunization using a mixture of A β ₁₋₄₀ and A β ₁₋₄₂ peptides without adjuvant in PDAPP transgenic mice. Two additional studies demonstrated that A β vaccination in transgenic CRND8 or APP/PS1 mice strongly improved behavioral performance in learning and memory tasks. Subsequently, different research has confirmed the A β -lowering effect of A β vaccination in AD-like transgenic mouse models. Illustration of the effect of A β immunotherapy on plaque deposition demonstrated below. We intranasally immunized 1 month-old J20 hAPP tg mice with full-length A β _{1-40/42} and an adjuvant, E. coli heat labile enterotoxin LT(R192G), for 11 months. Abundant plaque deposition was seen in hippocampus and cortex of untreated, age-matched control J20 mice however, A β -immunized J20 mice had almost no plaque deposition. Small punctate dots of A β immunoreactivity remained, often adjacent to blood vessels, possibly indicating clearance. It is clear from this and many other studies that immunizing APP transgenic mice prior to plaque deposition strongly prevents plaque deposition.

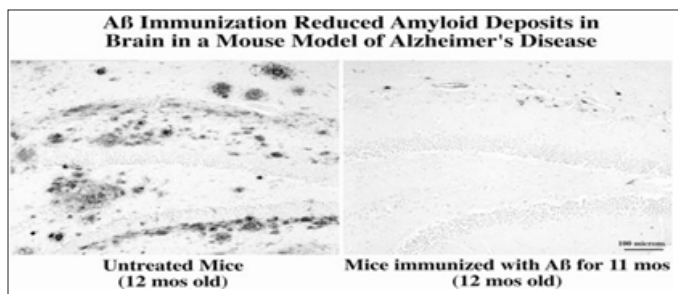


Figure 1: Immunization with full-length A β dramatically reduced cerebral A β plaque burden in J20 hAPP transgenic mice, a mouse model of Alzheimer's disease

In this review, 1 mo-old mice were primed by giving an intraperitoneal injection of 100 μ g A β _{1-40/42} synthetic peptide plus 50 μ g Complete Freund's adjuvant. The mice were then boosted weekly by intranasal application of 100 μ g A β _{1-40/42} plus 5 μ g adjuvant LT (R192G) for a total of 11 months and euthanized at 12 months, an age in which these mice typically accumulate many plaques in cortex and hippocampus (left panel). Immunohistochemical analysis with an A β -specific polyclonal antibody R1282. Dennis Selkoe et al revealed a significant reduction in plaque burden in cortex and hippocampus (shown in right panel). Scale bar: 100 μ m [2]. [Adopted with permission from Lemere, C.A., Maier, M., Jiang, L., Peng, Y., Seabrook, T.J. Amyloid-beta immunotherapy for the prevention and treatment of Alzheimer's disease: Lesson from mice, monkeys and men. *Rejuvenation Research* 9:77-84, 2006.

Different studies about passive immunization studies using A β antibodies against the N-terminus, mid-domain, and C-terminus of A β have been used in transgenic mice with AD-like pathology. Bard et.al performed passive immunization in PDAPP mice using several different monoclonal anti-A β antibodies that targeted various A β epitopes and represented different IgG isotypes [3]. The A β antibodies were able to enter the central nervous system (CNS), bind plaques and induce clearance of pre-existing amyloid.

Later, the authors also stated that antibodies against the N-terminus of A β (3D6 against A β ₁₋₅ or 10D5 against A β ₃₋₇) were the most effective at reducing brain amyloid. Passive immunization of PDAPP transgenic mice with the 10D5 antibody led to reduced plaque burden, increased peripheral A β , improved hippocampal long-term potentiation (LTP), and improved cognitive performance and quality of life. Another monoclonal A β antibody, BAM-10 (A β ₁₋₁₂), reversed memory impairment in APP transgenic mice, even in the absence of significant amyloid reduction.

Microhemorrhage has been studied following passive immunization with N-terminal A β antibodies in APP transgenic mice. In contrast, passive immunization with m266, a central domain A β monoclonal antibody, did not increase microhemorrhage in mouse brains, although it significantly decreased A β plaque pathology and improved cognition. In addition, passive immunization with C-terminal A β antibodies has been reported. Bard et al first reported that the 16C11 antibody (against A β ₃₃₋₄₂) failed to lower plaque burden or improve cognitive deficits [4]. Wilcock et al found that transgenic 2576 transgenic mice that were immunized with 2286, an IgG1 C-terminal A β antibody against A β ₂₈₋₄₀, for 3 months showed an improvement in alternation performance in the Y maze, a reduction in both diffuse and compact amyloid deposits, and transient but significant microglial activation. However, this same C-terminal antibody led to a significant increase of CAA-associated microhemorrhage in immunized mice. Subsequently, an IgG2b C-terminal antibody (2H6) and its de-glycosylated version (de-2H6) were shown to reduce A β pathology and significantly improve performance in a radial arm water maze. Vascular amyloid and microhemorrhages were reduced in de-2H6-vaccinated mice, possibly because deglycosylation of the antibody decreased its affinity for the Fc γ receptor.

Evidence of active A β vaccination in rhesus monkeys

monkeys Using APP transgenic mouse models for the study of A β immunotherapy has the limitation that the immune response elicited is directed to transgene-expressed human A β but not endogenous mouse A β protein in brain. Therefore, a preclinical model that is genetically similar to humans, exhibits A β pathology with normal aging, and has a comparable immune response, would be of benefit for testing the safety and efficacy of an A β vaccine before transitioning to human clinical trials. Rhesus monkeys species, a form of non-human primates such as *Macaca mulatta* and Caribbean vervets exhibit age-related A β deposition similar to AD in humans. Pilot study of vervets of A β vaccination in 6 aged demonstrated that active immunization with aged A β _{1-40/42} over ten months produced appreciable titers of plasma A β antibodies that recognized plaques in human, vervet, and APP transgenic mouse brains. Anti-A β titers were approximately 1000-fold lower in cerebrospinal fluid (CSF) compared to titers in plasma. In addition, A β protein levels in plasma were elevated while those in CSF and brain tissues were reduced in vaccinated vervets. Inflammation and T cells were absent in the brain tissues of immunized vervets.

Another pilot study revealed in rhesus monkeys using a similar active vaccine with aggregated A β ₁₋₄₂ or aggregated islet amyloid polypeptide (IAPP) and CFA was investigated. Rhesus monkeys that received aggregated A β ₁₋₄₂ generated moderate anti-A β titers as well as a 5-10 fold increase of A β levels in plasma, as compared with the rhesus monkeys that were vaccinated with aggregated IAPP. In contrast to previous vaccination studies in vervets, cerebral A β levels in these younger monkeys was not reduced even though plasma A β levels were elevated after vaccination possibly, because they had not reached a plaque-bearing age. Together, these two studies demonstrate that non-

human primates display natural A β deposition with aging and generated anti-A β antibodies when actively vaccinated with an A β peptide.

Active and passive A β immunization: Evidence from human clinical trials

Elan/Wyeth in 2000 and 2001 carried out extensive preclinical studies of active immunization with pre-aggregated A β showed promising benefits such as stimulating high anti-A β antibody titers in plasma, and consequently reducing cerebral A β burden, as well as preventing or reversing cognitive decline in different mouse models. After a single-dose Phase I study in 24 patients and a multiple-dose Phase I study in 80 patients with mild to moderate AD in the United Kingdom, the immunization of A β 1–42 peptide (AN1792) in combination with the adjuvant QS-21 showed good tolerability in patients and, 58% of the patients with multiple-dose vaccination developed an anti-A β humoral response. Elan/Wyeth further stated that there were few adverse effects and some evidence of possible improvement in one of the clinical measurements. Next, a Phase IIa study was initiated in which 372 mild to moderate AD patients were enrolled to receive either AN1792 (300 patients) or placebo (72 patients). The trial was stopped due to the development of meningoencephalitis in 18 of the 300 (6%) immunized AD patients. Although the adverse events correspond not to antibody response, it has been suggested that they may have been initiated by activation of cytotoxic T cells and/or autoimmune reactions. Subsequent reports showed that even brief active immunization with AN1792 succeeded to some degree in generating an anti-A β antibody response, clearing A β from brain, and modestly stabilizing cognitive function. However, Holmes and colleagues reported that small group of immunized AD patients who came to autopsy several years after the trial was stopped showed no significant differences between placebo and AN1792 vaccinated groups in survival outcomes or time to severe dementia, or in cognitive measures, even though large areas of cortex were devoid of amyloid plaques. It is quite possible that the disease process, including synaptic and neuronal loss, was too far along when these AD patients entered the trial, suggesting that A β vaccination may have its best effects if given prior to or in the very early stages of AD. Active A β vaccine trials are current underway, sponsored by pharmaceutical companies such as ELAN/Wyeth, Novartis, Merck, Affiris, and United Biomedical.

Direct injection of anti-A β antibodies may be an easy and relatively safe method to provide A β antibodies without eliciting Th1-mediated autoimmunity. Intravenous immunoglobulin (IVIg) antibodies, a pooled mixture of human antibodies including anti-A β antibodies, were found to interfere with the oligomerization and fibrillization of A β peptide protect neurons exposed to toxic concentrations of A β peptide and promote the clearance of A β peptide from the brain, suggesting that IVIg treatment may be useful in humans as a type of passive immunotherapy to treat AD. In a small pilot study IVIg reduced A β peptide levels in the CSF and significantly increased the A β levels in blood, suggesting that the antibody mixture induced efflux of A β from the brain to the periphery. Furthermore, some improvement in cognitive function was seen in immunized patients in the absence of adverse events. Anti-A β antibodies were detected in CSF of the patients subsequent to IVIg treatment, indicating that IVIg antibodies may cross the blood- brain barrier (BBB) and thereby affect A β levels in the brain. Several other clinical trials have shown evidence of the potential of IVIg immunotherapy for AD but these trials were carried out only in only a small number of AD patients. More recently, larger phase III clinical IVIg trial in AD

patients was initiated by Baxter Biosciences and the Alzheimer's Disease Cooperative Study (ADCS). In addition, other passive A β vaccine clinical trials are underway, sponsored by pharmaceutical companies such as ELAN/Wyeth/Janssen, Eli Lilly, Pfizer, Hoffman-LaRoche, Genentech, and GlaxoSmithKline.

Immunotherapeutic Strategic A β epitope-specific vaccines

The use of N-terminal A β derivatives as immunogens was hypothesized to generate a strong humoral immune response while avoiding a deleterious A β -specific T cell response because the dominant B cell epitope for anti-A β antibodies generated by active immunization with full-length A β was found to reside within the first 15 amino acids of the A β N-terminus, which was later refined to A β 1–5, 1–7, 1–8, 1–9, 1–11, 1–16, 4–10, and Ab3–7 in mice, A β 1–7 in vervets, and A β 1–18 in humans while dominant A β T cell epitopes have been mapped to A β 6–28 or beyond A β 1–15 in mice and A β 16–33 in humans. This hypothesis has been confirmed by several groups using short A β fragment active vaccines. AD transgenic mice immunized with K6A β 1–30-NH2 vaccine containing 6 lysines linked to the first 30 residues of A β , K6A β 1–30[E18E19] vaccine with mutations at positions 18 and 19, PADRE-A β 1–15 epitope vaccine containing the A β 1–15 in tandem with the synthetic pan HLADR-binding peptide (PADRE) or another epitope vaccine composed of two copies of A β 1–11 fused with PADRE resulted in generation of anti-A β antibodies, reduction in plaque burden and/or cognitive impairment, and reduction or abolishment of autoreactive T cell responses. We found that while A β 1–15 peptide was less immunogenic than A β 1–40/42 for antibody production in wild-type mice intranasal boosting with dendrimeric A β 1–15 (16 copies of A β 1–15 on a lysine tree; dA β 1–15) and a mucosal adjuvant after a single priming injection of A β 1–40/42 in J20 hAPP mice resulted in high anti-A β antibody titers and reduced cerebral amyloid plaque burden. Later, we found that intranasal delivery of dA β 1–15 with LT(R192G) without a priming injection, also induced robust anti-A β titers and lowered cerebral A β levels and plaques in the brains of J20 APP tg mice without inducing an A β -specific cellular immune response. Intranasal delivery of 2 short A β immunogens, 2xA β 1–15 and R2xA β 1–15 (tandem repeat of A β 1–15 linked by 2 lysine residues, without or with an RGD motif at the N-terminus, respectively) resulted in high anti-A β antibody titers without an A β -specific T cell response, and reduced plaque load. In the case of the 2xA β 1–15 vaccine, improved memory acquisition in the Morris water maze in J20 APP tg mice was observed. Numerous other short A β fragment active vaccines are currently under investigation.

A β DNA vaccines

DNA vaccination may have potential as a treatment for AD because it is simple, easily modified, and may not require the use of an adjuvant. Immune responses of the host can be easily manipulated to obtain a Th2-type reaction. Initially, A β DNA vaccines were produced using adeno-associated virus vectors or adenovirus vector. Recently, researchers have focused on developing non-viral plasmid vectors because such DNA vaccines can be mass-produced at a low cost and have no possibility of viral infection or transformation.

Studies suggests A β 1–42 DNA vaccination with or without adjuvants has been shown to be efficient for breaking host A β 1–42 tolerance and inducing a Th2 immune response significantly reducing the cerebral A β burden in different AD-like transgenic mouse models and reducing CAA, high-molecular-weight

oligomers, and A β trimers in TgCRND8 mice. Movsesyan et al investigated a shorter DNA epitope vaccine containing three copies of A β 1–11 fused with a foreign T helper epitope (PADRE), and linked to macrophage-derived chemokine (MDC/CCL22) or three copies of Complement 3d (3C3d) for adjuvant activity. Vaccination of 3xtransgenic-AD mice (encoding mutant human APP, PS1 and Tau) with the pMDC-3A β 1–11-PRE construct led to high titers of Th2-biased anti-A β antibodies. A β pathology and glial activation were diminished in the absence of microhemorrhage and cognitive deficits were improved. The 3A β 1–11-PADRE-3C3d construct resulted in similar beneficial effects on antibody response and A β burden.

Okura studies revealed the immunized APP23 transgenic mice with non-viral A β DNA vaccines prior to A β deposition (prevention) or after the onset of A β deposition (therapy) in the brain. Cerebral A β burden was reduced in immunized mice following the prevention trial. Cerebral A β burden was reduced ~ 50% by the age of 18 months in the therapeutic trial. Neuroinflammation and T cell responses to A β peptide were absent in immunized APP23 and wildtype mice, even after long-term vaccination.

Routes administration of active A β immunization

Another strategy to increase the generation of A β antibodies and the safety of active immunization is to optimize administration routes of the vaccine delivery. For example, we demonstrated that intranasal administration of A β peptides, in the absence of adjuvant, induced a modest anti-A β antibody response sufficient enough to significantly reduce cerebral A β levels in PDAPP mice. Later, we found that adjuvant, *E. coli* heat labile enterotoxin LT (R192G), significantly enhanced anti-A β antibody generation in wildtype and APP tg mice when short A β peptide immunogens, dA β 1–15 [66] and 2xA β 1–15 were delivered intranasally. In both studies, intranasal A β immunization using LT (R192G) led to a predominantly Th2-biased immune response and a lowering of cerebral A β in the absence of any adverse effects.

Transcutaneous immunization utilizes antigen presentation by Langerhans cells in the skin. Previously, we reported that transcutaneous immunization with dA β 1–15, but not A β 1–40/42, and the adjuvant LT (R192G) resulted in moderate Th2-biased anti-A β antibody titers in wildtype mice. Subsequently, Town and colleagues showed that transcutaneous immunization with A β 1–42 with cholera toxin adjuvant resulted in robust anti-A β antibody titers, reduced cerebral A β levels, and increased A β in blood, while avoiding T cell infiltration into brain and cerebral microhemorrhage.

An oral DNA vaccine consisting of an adeno-associated viral vector carrying A β cDNA (AAV/A β) without adjuvant induced the expression and secretion of A β 1–43 or A β 1–21 in transgenic 2576 mice, leading to the generation of long-lasting anti-A β antibodies. A single oral administration of AAV/A β to 10 month-old transgenic 2576 mice protected against progressive cognitive impairment and decreased A β deposition, insoluble A β , soluble A β oligomers (A β 56), microgliosis, and synaptic degeneration. Oral immunization of A β peptide-loaded microparticles also induced long-term anti-A β antibody production in female BALB/c mice.

Second-generation active A β vaccines in non-human primates and canines

Janus C, et al studies revealed the second-generation A β vaccines have been tested in several non-human primate species [5]. Non-human primates develop A β plaque deposition with aging, although

the degree of deposition varies among species. Administration of site-specific UBITH A β vaccine (A β 1–14) in baboons and macaques showed that N-terminal-directed anti-A β antibodies were generated while bypassing any adverse A β cellular immune responses. The vaccine showed significant efficacy in both non-human primate species, suggesting a potential versatility of the vaccine. Furthermore, anti-A β antibodies generated by vaccinated monkeys sequestered toxic A β from the CNS into the periphery. In addition, repeat dosing with the UBITH vaccine did not appear to be detrimental or toxic in macaques, indicating it was a safe and well-tolerated vaccine in adult macaques. Another recent evidence active A β vaccination study in lemurs showed that moderate to robust anti-A β IgM and IgG titers were generated in those lemurs immunized with several A β derivatives described above, K6A β 1–30 and K6A β 1–30[E18E19], with alum adjuvant. An increase of A β 1–40 in plasma suggested that resulting anti-A β antibodies may bind to A β in the brain and draw it to the periphery.

Similar to non-human primates, the A β gene in dogs is similar to human A β and aged canines, in particular, beagles, accumulate A β plaques in the brain with normal aging. Head and colleagues immunized aged beagles presumed to have cerebral A β deposition, with fibrillar A β 1–42 and alum. A β -vaccinated beagles generated strong anti-A β antibody responses and had reduced A β plaque load in several brain regions. However, A β vaccination in aged beagles did not ameliorate cognitive impairments, suggesting that early vaccination may be needed to see cognitive benefits.

Second-generation passive immunotherapy in murine models

Town T, et al. demonstrated passive A β immunization has been shown to have some beneficial effects on synaptic plasticity and neuronal function. Chauhan et al. also reported that intracerebroventricular (i.c.v.) infusion of A β antibodies protected APP transgenic mice from synaptic loss and gliosis [6]. Klyubin and co-workers reported that i.c.v. infusion of 4G8, a monoclonal antibody directed to the mid-region of A β (A β 17–24), prevented synaptic plasticity disruption induced by naturally occurring, cell-derived A β oligomers, and by human CSF containing A β dimers. A study by Spires-Jones et al. found that immunization with the A β monoclonal antibody 3D6 that recognizes the free N-terminus enhanced structural plasticity in PDAPP mouse brain.

Recent evidence suggests that A β oligomers (dimers, trimers, tetramers, etc.) rather than monomers or fibrils may be the major toxic agents that specifically inhibit LTP and synaptic plasticity in AD. As a result, there is a surge of passive A β immunotherapies focusing on inhibiting or reversing A β oligomerization using specific anti-oligomer antibodies. One example of an oligomer conformation-specific antibody, NAB61, was used to immunize aged transgenic 2576 mice and it showed significant improvement in spatial learning and memory, without altering brain amyloid deposition or APP processing. This result supports the hypothesis that cognitive deficits in APP tg mice are at least partially caused by toxic soluble A β oligomers.

Interestingly, Britschgi et al. recently reported that abundant natural, endogenous anti-A β antibodies (IgGs), especially those reactive against high molecular mass assemblies of oligomeric A β and pyroglutamate or oxidized residues of A β , can be found in plasma and CSF of both AD patients and healthy controls. Once isolated from human blood, these natural antibodies protected primary neurons from oligomeric A β toxicity in vitro. Plasma IgG reactivities against several A β forms, including oligomeric A β 1–42 in particular, as well as amyloidogenic non-A β peptides

were reduced with aging and AD in humans. In addition, natural A β IgGs observed in plasma samples from our aged vervets were similar to those in human AD patients. Active immunization with A β 1–40/42 in aged vervets led to high titers not only against conformation-specific A β assemblies, but also against non-amyloidogenic peptides. Thus, it appears that enhancing the generation of neuroprotective natural anti-A β antibodies or passive applying them to the elderly might be beneficial for the prevention and treatment of AD.

Arbel et al. reported a novel approach to inhibit A β production via antibodies against the beta-secretase cleavage site of the APP. Long-term systemic administration of this anti-beta-site antibody in Tg2576 mice improved cognitive deficits, reduced inflammation, and decreased the incidence of microhemorrhage without inducing any peripheral autoimmunity responses. However, cerebral A β levels were unchanged by the antibody treatment.

Alternative strategies to improve the efficacy of passive immunization and reduce its side effects have been reported. Compared with systemic immunization of A β Mab 6E10, prolonged i.c.v. infusions by osmotic mini-pump dose-dependently reduced the parenchymal plaque burden, astrogliosis, and dystrophic neurites at much lower doses. In addition, side effects observed after administration of some N-terminal A β antibodies such as microhemorrhage were reduced by modulating antibody dose deglycosylating whole IgG A β antibody removing the Fc portion by proteolysis to produce Fab'2 or designing recombinant Fab or single-chain variable fragment.

A β mechanism immunotherapy

Studies shows the mechanisms by which A β is cleared from the brain via active or passive vaccination are not clear yet, however, several major hypotheses have been proposed including microglia-mediated phagocytosis, antibody-mediated alterations of A β aggregation and neutralization of A β toxicity, peripheral sink, and intracerebral sequestration of A β in a monomeric state.

Microglia-mediated phagocytosis

Intracellular A β immunoreactivity within microglia and macrophage in PDAPP tg mice immunized with A β monoclonal antibodies indicated that peripherally administered A β antibodies can cross the BBB, bind to A β in plaques and trigger the Fc receptors (FcR)-mediated microglial phagocytosis. The mechanism of microglial FcR-dependent A β clearance was further proven in an ex vivo assay with sections of PDAPP tg or AD brain tissue. The data showed that antibodies against A β peptide activated microglial cells and subsequently removed plaques via Fc receptor (FcR)-mediated phagocytosis. Active vaccination with A β 1–42 in PDAPP tg mice and in AD patients also showed evidence that the reduction of compact and densely stained A β deposits were associated with microglial Fc-receptor phagocytosis. Additionally, the activation of microglial phagocytosis and removal of A β deposits were also observed in mice treated with A β nonviral DNA vaccines. The combined results of numerous active and passive A β immunotherapy studies indicate that FcR-mediated activation of microglia could be a central mechanism of reducing A β load in brain.

However, effective clearance of A β deposits were also observed in A β 1–42 immunized FcR γ ^{-/-} Tg2576 mice or in APP transgenic mice treated with F(ab')₂ fragments of 3D6 antibody (antibody without Fc portion) implying that the FcR-mediated phagocytosis is not the only mechanism involved in microglia-induced plaque removal. These findings demonstrate that Fc-independent mechanisms, in addition to Fc-dependent mechanisms, are capable

of mediating the effects of active and passive A β immunization.

Antibody-mediated alterations of A β aggregation and neutralization of A β toxicity

Certain anti-A β antibodies have been reported to directly bind to A β and either prevents oligomerization and fibril formation of A β or dissolve A β aggregates in vitro. Specific conformational A β antibodies target existing plaques in the brain and lead to direct disassembly in vivo. These findings suggest that direct interaction of anti-A β antibodies with A β could potentially affect A β aggregation both in vitro and in vivo. In addition, A β antibodies that recognize an oligomeric conformation have been shown to reverse or ameliorate the cognitive deficits in vivo, indicating that another possible mechanism of A β immunotherapy may be the blockade of neurotoxicity induced by A β oligomers.

A β clearance via peripheral sink

The peripheral sink mechanism was first proposed by DeMattos and colleagues in the study using m226, an A β mid-region antibody with a high affinity for soluble A β , in PDAPP tg mice. Later, this mechanism was confirmed by active [60, 61, 112, 113] and passive [30, 114–116] A β immunization studies. These studies suggest that A β antibody in plasma can reduce circulating A β level by directly binding to plasma A β , which in turn disrupts the brain-blood equilibrium of A β and drives the removal of soluble A β from the brain. Furthermore, the studies performed by Deane and colleagues indicate that net clearance can involve a peripheral sink effect and an active FcR-mediated process at the BBB as well.

Intracerebral sequestration of monomeric A β

Another mechanism, intracerebral sequestration of monomeric A β , has been proposed recently by Yamada and colleagues, who found that peripheral injection of anti-A β monoclonal antibody, m266, with high affinity to soluble A β , followed by intracerebral microinjection of radiolabeled A β 1–40 in wildtype mice slowed A β clearance from mouse brains. In addition, peripheral administration of m266 antibody in young, pre-plaque APP transgenic mice led to increased levels of monomeric, antibody-bound A β in brain without affecting total soluble A β levels in brain. Their results indicate that certain A β antibodies may sequester soluble, monomeric A β in the brain thereby preventing the formation of multimeric A β and related neurotoxicity.

Another mechanisms

McLaurin J, et al stated that antibody-independent immune cell-mediated plaque clearance, effects on A β -mediated vasoconstriction, and modulation of CNS cytokine production as well as IgM-mediated hydrolysis of A β may be other possible mechanisms underlying A β immunotherapy. Overall, as illustrated in Fig. (2), there may be many mechanisms involved in A β clearance and cognitive improvement resulting from active and passive immunization. These mechanisms may act independently, concomitantly or sequentially for A β immunotherapy depending on the severity of the disease, antibody specificity and Ig isotype, and specific animal model used.

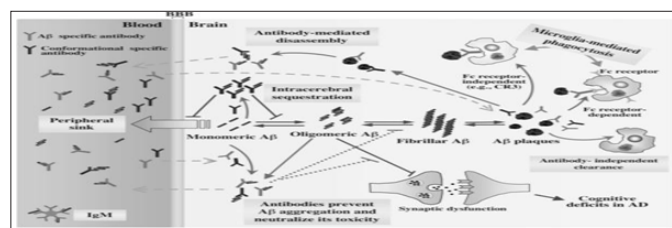


Figure 2: Potential mechanisms underlying A β immunotherapy in AD models

Antibody-mediated microglial FcR-dependent and FcR-independent clearance of plaques by phagocytosis; antibody-mediated direct disassembly of plaques; prevention of A β aggregation and neutralization of oligomer toxicity; peripheral sink effect by clearance of circulating A β ; intracerebral sequestration of A β in a monomeric state; hydrolysis of A β by IgM; and antibody-independent, cell mediated plaque clearance have all proposed to play roles in the removal of A β from the brain by A β immunotherapy in AD models. These potential mechanisms may act concomitantly or sequentially and play independent roles depending on the stage of AD pathogenesis and type of antibody, as well as the specific animal model used.

Conclusions

Evidence from animal model and human shows effectiveness of A β immunotherapy in AD patients. Studies evidence revealed the induce anti-A β antibody generation, reduce cerebral A β levels, and in some studies, stabilize or improve cognition. Evidence from the AN1792 trial, many groups, both academic and commercial, has generated novel active and passive A β vaccines. The goals of passive A β immunization are to lower safely cerebral A β via monthly injections of antibodies. The goals of active A β immunization are to induce long-lasting, safe, and cost-effective vaccines to lower cerebral A β and/or prevent A β aggregation. The ultimate goal for both types of vaccines is to prevent or diminish the downstream effects of A β on synapses and neurons, thereby providing cognitive benefits. Multiple active and passive A β immunotherapy clinical trials are currently underway. In addition, tau-related vaccines are also being studied in tangle-bearing tau transgenic mouse models. As the average lifespan increases worldwide, the number of AD patients who suffer from this devastating neurodegenerative disease grows as well. Therefore, it is necessary to find a safe and effective way to prevent or cure the disease as soon as possible. Although there is much work to be done, we remain hopeful that A β immunotherapy, either alone or in combination with other therapies, will succeed in preventing or treating AD [7-64].

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