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Amyloid vaccine for Alzheimer's disease: Is it feasible?

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Abstract

Alzheimer's disease (AD) is the most common neurodegenerative disorder and the most prevalent cause of dementia with ageing in the world. The social and economic burdens of AD continue to rise. In 2010, an estimated 36 million people worldwide were living with dementia— a number that is projected to increase to 66 million in 2030, and to 115 million in 2050. The basic pathological mechanism in these disorders is a conformational change of a normal protein expression. Aβ form neuritic, plaques deposits and cerebral amyloid angiopathy, and hyperphosphorylated tau aggregates within neurons as paired helical filaments in neurofibrillary tangles. New therapeutic approaches targeting β-amyloid (Aβ) have been discovered and developed with the hope of modifying the natural history of Alzheimer's disease (AD). Researches are still being carried on to see the feasibility of these vaccines for AD.

Key Words:
Alzheimer's disease, Vaccine, β-amyloid, Immunization

"Alzheimer's is the cleverest thief, because she not only steals from you, but she steals the very thing you need to remember what's been stolen. "—Jarod Kintz

Alzheimer's disease (AD), first described by German psychiatrist and neuropathologist Alois Alzheimer in 1906 and was named after him, is the most common form of dementia. The disease has no cure and it worsens as it progresses leading to death. New Alzheimer's treatments are now in progress. Researches are being carried on to develop target microscopic clumps of the protein beta-amyloid (plaques). Two strategies aimed at beta-amyloid include immunizing the body against it and blocking its production are used for the cure of AD. The following article reviews the studies targeted at developing vaccines to treat AD and highlights the feasibility of it.

In a study by Scarpini et al (2003) it was stated that pharmacological treatment of AD is based on the use of acetylcholinesterase inhibitors, with beneficial effects on cognitive function and behavior but their role in AD pathogens was unknown. Some potentially disease modifying treatments which included amyloid-β-peptide vaccination, cholesterol-lowering agents, secretase inhibitors, chelating agents, and anti-inflammatory drugs were also reported to be used for the disease.

Vaccines were employed to cure AD. Several studies and experiments were done to check the feasibility of the vaccines. A study done by Hock C. et al (2003) tested

whether antibodies against β-amyloid were effective in slowing progression of Alzheimer's disease. Cognitive functions of 30 patients were assessed who received a prime and a booster immunization of aggregated Aβ42 over a 1 year period in a placebo-controlled randomized trial. Out of 30 patients, 20 were found to generate antibodies against β-amyloid, as determined by tissue amyloid plaque immune-reactivity assay and showed significantly slower rates of decline of cognitive functions and activities of daily living (as indicated by the Mini Mental State Examination, the Disability Assessment for Dementia, and the Visual Paired Associates Test of delayed recall from the Wechsler Memory Scale) as compared to patients without such antibody formation. Two of three patients who had experienced transient episodes of immunization-related aseptic meningo-encephalitis also showed these beneficial clinical effects.

The study by Lemere C. et al (2001) was done on transgenic mice and reported that vaccination with Aβ resulted in improvement in their cognitive deficits and significant lowering of the Aβ burden in the brains of Amyloid Precursor Protein (APP) transgenic mice. It was a novel approach which described mucosal (intranasal) Aβ vaccination. The details of the pathology of how Aβ vaccination chronically lowers Aβ levels and reduces Aβ remains unclear. An active vaccine (AN1792) was discontinued in 2002 due to occurrence of meningo-encephalitis in around 6% of patients. Other second-generation active Aβ vaccines and passive Aβ immunotherapies have been developed and are under clinical investigation with the aim of accelerating Aβ clearance from the brain of AD patients. The most recent and advanced of these immunological approaches is bapineuzumab which is composed of humanized anti-Aβ monoclonal antibodies that has been tested in two Phase II trials. This will reduce Aβ burden in the brain of AD patients. There is also uncertainty of its preliminary cognitive efficacy. Also, vasogenic edema may limit its clinical use in the near future. The results of four ongoing large Phase III trials on bapineuzumab will soon provide answers regarding whether passive anti-Aβ immunization is able to alter the course of this devastating disease (Panza F. 2010).

Another study found out that some plaque clearance and modest clinical improvements were observed in patients following immunization. As a result of the following study, at least 7 passive Aβ immunotherapies and several second-generation active Aβ vaccines are now in clinical trials in patients with mild and moderate AD. Data obtained from preclinical studies and clinical trials has found out that Aβ immunotherapy might be the most effective in preventing or slowing the progression of AD when patients are immunized before or in the very earliest stages of disease. Imaging technology and biomarkers for AD have improved greatly over the past 10 years and in the future, might be helpful to identify pre-symptomatic or at-risk individuals who might benefit from Aβ immunization (Lemere C. & Masliah E. 2010).

Chackerian B. et al (2006) has stated in her study that a recent clinical trial of a candidate Aβ vaccine has suggested that it is important to develop techniques to induce high titer antibodies against Aβ associated with vaccine efficacy while reducing the T cell responses against Aβ

that were potentially responsible for serious side effects. Also, immunization with self- and foreign antigens arrayed in a repetitive fashion on the surface of virus-like particles (VLPs) induces high titer antibody responses at low doses and in the absence of potentially inflammatory adjuvants. In her study, she examined the antibody and T cell responses upon immunization with human papillomavirus VLP- and Qβ bacteriophage-based Aβ vaccines. The study showed that immunization with Aβ conjugated to VLPs or Qβ elicited anti-Aβ antibody responses at low doses and without the use of adjuvants. The reason behind it was the flexibility of these virus-based display systems which allowed the authors to link and induce antibodies against short Aβ-derived peptides from the amino- and carboxyl-termini of the peptide. Another research conducted by them on immunization of mice with Aβ peptide in combination with Freund's adjuvant elicited predominantly IgG2c antibodies and strong T cell proliferative responses against Aβ. In contrast, VLP-conjugated Aβ peptides elicited more balanced isotype responses, dominated by IgG1. The result of both the researches was that both VLP and Qβ-based Aβ vaccines induced weak or negligible T cell responses against Aβ. Hence, virus-based vaccines that allow the presentation of Aβ in a repetitive dense array are new and potentially more effective vaccine candidates for Alzheimer's disease.

But for human beings, the efficiency of this therapeutic strategy has to take into account the specificities of human amyloid, especially at the early stages of 'sporadic' Alzheimer's disease (AD). Chackerian B (2006) conducted another study where Aβ 40/42 were previously quantified in tissues from well-established brain bank, including individuals without dementia; with both mild amyloid and tau pathologies, corresponding to the earliest stages of AD pathology. A proteomic method combined with western blotting and mass spectrometry for the characterization of insoluble Aβ extracted in pure-formic acid was adapted for it. The result was that the amino-truncated Aβ species represented more than 60% of all Aβ species, not only in full blown AD, but also at the early stage of AD pathology. At this stage, Aβ oligomers were exclusively made of Aβ-42 species (most of them being amino-truncated). Thus it was proved that amino-truncated Aβ-42 species were instrumental in the process of amyloidosis. In conclusion, a vaccine which specifically aims to target these pathological amino-truncated species of Aβ-42 were likely to be highly beneficial, by inducing the production of specific antibodies against pathological Aβ products that are involved in the early and basic pathology of amyloidosis in humans (Sergeant N. et al, 2003).

The agents that are available at present for the management of Alzheimer's disease treat only the symptoms of neuro-degeneration and results in short-term improvements in cognitive function. Immunotherapy has become one of the first tests of the amyloid hypothesis in the clinic, and is an evolving approach to the treatment of Alzheimer's disease that offers a genuine opportunity to modify the progress of the disease. Although initial clinical trials of one approach met with some setbacks, active or passive immunization holds great potential for treating and preventing Alzheimer's disease (Schenk D. 2002). *As a writer, I have to admit, there is something darkly compelling about*

Alzheimer's because it attacks the two things most central to a writer's craft - language and memory, which together make up an individual's identity. Alzheimer's makes a new character out of a familiar person.

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