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Mini Review

Development of Alzheimer's Disease Vaccines: a Perspective

Marciani DJ*

Qantu Therapeutics, USA

***Corresponding author:** Marciani DJ, Qantu Therapeutics, Inc. 612 E Main Street, Lewisville, TX 75057, USA

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Abstract

Like infectious disease vaccines, effective Alzheimer's disease vaccines should elicit an antibody response similar to the natural autoantibodies found in serum and preparations of intravenous immunoglobulins, which recognize an array of amyloid-β conformations. An immune response that is the result of a progressive formation over time of antibodies against toxic amyloid-β conformations and that different from most vaccines under development, would require the whole protein as an antigen, including both B and T-cell epitopes. However, due to the presence of amyloid-β T-cell epitopes and the fact that such a protein is a Th1 immune modulator, safe and effective vaccines, besides eliciting Th2 immunity, should inhibit but not abolish Th1 immunity, which is needed for protection against pathogens; a strategy that would apply to other potential Alzheimer's disease vaccine antigens, e.g. tau. Due to immunosenescence, these vaccines would be more effective for preventive rather than therapeutic purposes, as younger individuals produce a better immune response. Recently developed novel adjuvants that most probably act at the dendritic cell level and that can deliver such a selective Th2 immune modulation while inhibiting Th1 immunity, would be crucial for the development of these proposed vaccines.

Keywords: Alzheimer vaccine; Amyloid-beta; Intravenous immunoglobulin; Immunotherapy

Abbreviations

AD: Alzheimer's disease; Aβ: Amyloid-β; $Aβ_{42}$: Whole Aβ; DC: Dendritic Cell; Nabs: Natural Antibodies; IVIG: Pooled Immunoglobulins; mAb: Monoclonal Antibodies

Introduction

Due to the high prevalence of Alzheimer's disease (AD), 5.2 million cases in the US alone, which is expected to triple by the year 2050 to 16 million, it is apparent that an active immunization or vaccination to prevent and/or treat this disease would be the most effective way to manage it. Significant evidence supports the role of circulating antibodies against amyloid-β (Aβ) in preventing and/or reducing toxic extracellular Aβ oligomers, the main cause of AD [1-3]. Indeed, Schenk et al. showed that vaccination of a transgenic mouse model for AD with whole Aβ ($Aβ_{42}$) and the Th1 adjuvant QS-21, prevented plaque formation and attenuated behavioral deficits [4,5]. However, clinical studies with a similar vaccine, AN-1792, resulted in serious side effects and some deaths, caused by a damaging Th1 inflammatory immune response elicited by the $Aβ_{42}$'s T-cell epitopes plus QS-21 [6,7]. Hence, to prevent a harmful Th1 immunity, later AD vaccines contained truncated Aβ antigens without T-cell epitopes, usually combined with Th1 adjuvants, a strategy that has yielded disappointing results in clinical studies (http://www.clinicaltrials.gov) [8-11]. While it was assumed that truncated Aβ with Th1 adjuvants elicits a safe immune response, these adjuvants induce a systemic Th1 immune response that could affect microglia, magnifying the neuroinflammation linked to AD [12-15]. This situation may also occur also with other likely antigens for AD vaccines, as with the tau protein, where the whole protein or some of its peptides with Th1 adjuvants may trigger a damaging inflammatory response [16,17]. Hence, there is a need to reassess the current AD vaccine paradigm and consider new approaches to its development.

Different from infectious disease vaccines where the number of Th1 adjuvants is large, vaccines against neurodegenerative proteinopathies, like AD, have a negligible selection of adjuvants that stimulate solely Th2 immunity, alum being the most common [18]. Still, that alum does not elicit an effective immunity in the elderly, as shown by the age-associated decrease in the efficacy of the flu and other vaccines [19] and have cumulative neurotoxicity [20], would preclude its use in AD vaccines. That certain bacterial toxins are "conditional" Th2 adjuvants, i.e. the stimulated immunity would depend on the age and mode of administration among other factors, adds an element of risk when used in large populations; for example, cholera toxin elicits Th2 immunity in young animals, but induces Th1 immunity in older ones [21], as well as a Th17 immune response [22]. The recent reports that some well-defined helminth glycans and plant-derived glycosides elicit Th2-only immunity [18,23], despite the absence or presence of T-cell epitopes, offer a new approach to develop safe and effective AD vaccines. Access to adjuvants that stimulate Th2 but inhibit Th1 immunity would allow the use of whole proteins, e.g. $Aβ_{42}$ and tau; antigens that are not used because of the damaging inflammatory immune response caused by their T-cell epitopes. Significantly, since $Aβ_{42}$ has an intrinsic Th1 immune modulatory activity [24,25], the use of adjuvants that inhibit Th1 immunity will be essential with this antigen.

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Truncated Aβ antigens lacking T-cell epitopes and representing 25 to 36% of the whole protein [8-11], i.e. the B cell epitopes within the first 15 amino acids, while safer do not allow i) the formation of conformational epitopes [26-29] and production of antibodies against those epitopes that may be important for $A\beta_{42}$ disaggregation, and ii) the potential cooperativity between antibodies recognizing different epitopes [30]. Indeed, the epitopes targeted by most natural anti-Aβ antibodies (Nabs) include the T-cell epitopes' sequences [31,32], which for safety are absent in truncated Aβ [1-3]. This diversity of epitopes support the fact that $A\beta_{42}$ is not a "static" structure, but a dynamic one with conformations and oligomerization states that change with time and progression of the disease, a condition that is shown by the presence of Nabs targeting diverse $A\beta_{42}$ conformations [27,33,34]. Hence, it is improbable that truncated Aβ would deliver the broad selection of Nabs elicited by the polymorphic $A\beta_{42}$, some of which may play a role in the elimination of this protein's toxic forms. Although, the evidence implies that various Nabs are conformation-dependent and sequence-independent [26-29,35,36], it is obvious that the $A\beta_{42}$ primary structure, including T and B-cell epitopes, is driving this protein's folding and oligomerization, leading to formation of the conformational epitopes needed to stimulate production of conformation-dependent Nabs . An advantage of Nabs is that they can recognize "toxic" conformations of other proteins capable of forming amyloids [35,36]. However, that the conformation dependent antibodies induced by aggregated $A\beta_{42}$ apparently bind better to amyloids from this protein than other proteins, upholds the use of this protein as a vaccine antigen [35]; an observation that can be extended to other proteins forming amyloids. Yet, the stimulation of Nabs production cannot be attained with Th1 adjuvants without generating damaging pro-inflammatory responses, notwithstanding that $A\beta_{42}$ alone seems to be an effective Th1 immunity inducer [24,25,37,38]; hindrances that can be prevented by using adjuvants that solely stimulate Th2 while inhibiting Th1 immunity [18,23].

Although clinical evaluations of passive immunotherapy with pooled immunoglobulins from healthy donors (IVIG) containing various Nabs have not met the studies' primary outcome objectives, pre-clinical and clinical studies have shown some immune modulatory properties relevant to the treatment of neurodegenerative disorders [39-42]. Indeed, it has been shown that previous treatment with IVIG reduces the risk of AD by 42% [43]. While polyclonal IVIG preparations meet some standardization requirements due to the heterogeneity of their source and processing, they differ in their distribution of antibody's isotypes, and their binding to different regions of $A\beta_{42}$ and tau [44-47]. For example, IgM antibodies that catalyze the degradation of $A\beta_{42}$ and presumably tau, preventing their aggregation and toxicity, are inactivated during IVIG preparation; a situation that results in preparations containing different levels of specific antibodies [45,48-50]. Screening of IVIG preparations has shown that Nabs target the $A\beta_{42}$ region between residues 28-40 where the T cell epitopes are located, as well as pathogenic conformation; but poorly recognize the N-terminal fragment, which is the basis for most of the AD vaccines under development [31,32]. Yet, immunization with $A\beta_{42}$ in the AN-1792 vaccine study mainly yielded antibodies against the N-terminal region [8,51]; however, the damaging pro-inflammatory response induced by this vaccine [6] and the increase in Th1 cytokines in mice immunized with $A\beta_{42}$ without an adjuvant [24,25], indicate that the $A\beta_{28-40}$ peptide region has an intrinsic Th1 immune modulatory activity. In effect it has been shown that Dendritic Cells (DCs) generated *in vitro* in the presence of $A\beta_{42}$ show an increase in the production of inflammatory molecules [52], which would aggravate AD. Thus, because of the likelihood that the Aβ regions containing T cell epitopes would induce Th1 inflammatory responses, even without adjuvants, the use of $A\beta_{42}$ as an antigen would require vaccine formulations that prevent Th1 immunity while stimulating antibodies' production.

The fact that Nabs target various $A\beta_{42}$ epitopes suggests cooperative effects between different antibodies, where binding of a Nab causes $A\beta_{42}$ conformational changes that allow binding of other antibodies [30], a process that may facilitate the disaggregation and degradation of the protein, which may also be extended to antigens like tau. The fact that two anti-Aβ monoclonal antibodies (mAbs), solanezumab that binds to the central region, and crenezumab a conformational antibody, failed to recognize Aβ in human brain tissue, has been explained as result of the mAbs' lack of specificity [53]. Another explanation may be that some mAbs require other antibodies to exert their action via cooperative effects. Nevertheless, IVIG studies strengthen the notion that the production of an effective, protective array of Nabs requires $A\beta_{42}$ rather than its fragments, to obtain antibodies against both linear and conformational epitopes, including catalytic antibodies [54]. While linear epitopes can be readily available by using Aβ fragments [55,56], the fact that the delivery of conformational epitopes that include T cell epitopes are apparently necessary for a "protective" immunity, is more challenging due to the myriad of $A\beta_{42}$ non-covalently bound aggregates that can be reorganized depending on various factors. Even so, there are several Aβ constructs apparently with the desired conformations needed to develop effective vaccines [55-58] that can be readily synthesized. Another approach could be the use of DNA vaccines encoding for $A\beta_{42}$; however, attaining an effective immune response would require a prime boost of $A\beta_{42}$ with Quil A, a strong Th1 adjuvant [38]. Of interest is that wild-type mice immunized six times with human $A\beta_{42}$ plus 20 μg of Quil A, did not develop neuroinflammation [59], results that contrast with those of the human AN-1792 vaccine having 50 μg of QS-21[6,7,60], a significantly less toxic compound than Quil A with a mouse acute toxic dose of over 250 μg [61]. While the difference between the immune responses in humans and mice cannot be explained by differences between the Aβs that are very similar, these results stress the need to avoid adjuvants that elicit even a poor Th1 immunity. However, regardless of the antigen's source, an effective AD vaccine should induce a broad immune response, which is analogous or better than that found in IVIG, which means eliciting antibodies targeting a variety of components from the Aβ cascade.

Similar to immunity against pathogens, the various anti-Aβ Nabs found in IVIG indicate previous exposure of the immune system to a broad variety of antigens. Thus, a successful AD vaccine would probably have an assortment of antigens, which besides Aβ-derived antigens may include tau as evidently there is synergism between this protein and Aβ in AD development [62-66]. Yet, the vaccine must elicit only Th2 without residual Th1 immunity; a difficult endeavor when considering the intrinsic $A\beta_{42}$ Th1 immune modulatory activity and limited access to Th2 adjuvants that inhibits Th1 immunity. Since AD shows a constant progression, its prevention/treatment could

require regular immunizations for the rest of the patient's life in order to sustain an effective level of protective antibodies against a diversity of antigens; a complex situation because of immunosenescence that affects the elderly population and increases inflammation [67]. An important observation for AD sub-unit vaccines is that prolonged immunization of aged dogs with $A\beta_{42}$ resulted in a drift of the antibody response from the linear epitopes of the amino terminus toward conformational epitopes [68]; an observation that may also be relevant to long-term immunization with $A\beta_{42}$ DNA vaccines [38]. This finding shows that regular vaccination with $A\beta_{42}$, probably for the rest of a patient's life, could stimulate the production of presumably protective antibodies that recognize new $A\beta_{42}$ abnormal conformations; an approach that in preventive AD vaccines could avoid or limit the need for a large number of $A\beta_{42}$ isoforms in the vaccine formulation.

From the available information it is possible to assume that to obtain an immune response similar to that from IVIG, an effective AD vaccine must have $A\beta_{42}$ and perhaps other relevant antigens, like tau, to stimulate the production of a broad array of protective antibodies. While a diverse antibody response may be attained by a prolonged vaccination schedule with $A\beta_{42}$ and/or a combination of Aβ antigens, a most likely situation with an AD vaccine would be the stimulation of only Th2 with the concomitant inhibition of Th1 immunity. This would be a prerequisite for the safe induction of humoral immunity without damaging inflammatory responses. Furthermore, because of the ageing recipient population, the vaccine should be able to ameliorate to some degree the immune system's decline, a result of immune senescence, in order to stimulate an effective immune response [18]. Consequently, it is evident that vaccines would be more effective to prevent than to treat AD, starting immunization when the immune system is still competent. To attain these objectives, the development of these vaccines would need, in addition to the antigens, unique immune modulators that would be different from those used in the infectious disease vaccines.

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