Journal of Neuroimmunology 287 (2015) 54–63

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Review article

Alzheimer's disease vaccine development: A new strategy focusing on immune modulation

Dante J. Marciani

Qantu Therapeutics, Inc., 612 E. Main Street, Lewisville, TX 75057, USA

ARTICLE INFO

Article history:
Received 19 March 2015
Received in revised form 5 August 2015
Accepted 6 August 2015

Keywords:
Alzheimer's vaccine
Adjuvants
Immunomodulation
Beta-amyloid
Tau protein
Fucosylated glycosides
Aldehydes

ABSTRACT

Despite significant advances in the development of Alzheimer's disease (AD) vaccines effective in animal models, these prototypes have been clinically unsuccessful; apparently the result of using immunogens modified to prevent inflammation. Hence, a new paradigm is needed that uses entire AD-associated immunogens, a notion supported by recent successful passive immunotherapy results, with adjuvants that induce Th2-only while inhibiting without abrogating Th1 immunity. Here, we discuss the obstacles to AD vaccine development and Th2-adjuvants that by acting on dendritic and T cells, would elicit regardless of the antigen a safe and effective antibody response, while preventing damaging neuroinflammation and ameliorating immunosenescence.

Contents

E-mail address: dmarciani@earthlink.net.

http://dx.doi.org/10.1016/j.jneuroim.2015.08.008
0165-5728/

1. Introduction

An effective way to control the epidemic of Alzheimer's disease (AD) that affects worldwide 40 million people and that is expected to double by year 2040, would be active immunization or vaccination; an approach supported by the presence of a natural immunity against AD (Britschgi et al., 2009; Magga et al., 2010; Dodel et al., 2011). Indeed, the positive results in the treatment of early AD obtained with the monoclonal antibody (mAb) aducanumab (Biogen), a replica of a protective antibody found in mentally competent elderly individuals that recognizes amyloid-β (Aβ) oligomers (Keller, 2015; Jeffrey, 2015), confirm the existence of that natural protective immunity. A development strengthened by the solanezumab (Eli Lilly) studies, a humanized mAb that binds monomeric Aβ, which apparently slows the disease progress [AAIC press release, July 22, 2015]. While antibody or passive immunotherapy can be an effective treatment for AD, supply and cost could limit its availability to the public; hence vaccination may be a practical way to prevent or delay the onset of this disease. Yet, because of immunosenescence or immune decline linked to aging, vaccination's efficacy should decline with age, a situation that may be corrected by switching to treatment with mAbs like aducanumab and solanezumab, which are independent of the immune system's competence.

Although AD vaccines started as therapeutics, because of immunosenescence and the disease's course, vaccination should be more effective in a preventive mode before or early in the disease. Yet, while studies with pre-symptomatic AD mouse and other animal models have shown promising results (Schenk et al., 2004; Wilcock et al., 2009; Lemere et al., 2004; Head et al., 2006), those results have not been translated into positive results in clinical trials (Delrieu et al., 2012; Karran, 2012). This situation has raised questions about the concept behind this approach (Morris et al., 2014; Lee et al., 2007; Foster et al., 2009), but with little consideration of the differences between the vaccines used in the AD mouse models and humans and the disparities in immunoresponse between species. Yet, passive immunotherapy has provided strong evidence that the immunological approaches may be the most effective and safe ways to deal with this disease.

While passive and active immunotherapies share similarities, they also have major differences. In prophylactic vaccination the immune system is induced to produce an antibody response against the epitopes critical for protection, a process that requires both an immunogen with all of the relevant epitopes and a competent immune system. Different from prophylactic vaccines, mAb therapy is not affected by immunosenescence, as the antibodies targeting specific epitopes are produced externally for administration to the patient. As mAb therapy should not produce immune regulators like cytokines, in principle there is no need for preventing a pro-inflammatory Th1 response, as required with prophylactic vaccination. Hence, there is a need for new paradigms in the development of this vaccine, which depart from the classic vaccines, e.g., infectious diseases and anti-tumor vaccines, where Th1 usually in conjunction with Th2 immunity, is the final objective. Indeed, AD vaccine development should aim to mimic the natural Th2 humoral immunity, rather than substituting it; a challenging task considering the different immunogens and the scarcity of adjuvants or immunomodulators that induce only an anti-inflammatory Th2 immunity.

2. Critical sub-unit vaccine components

2.1. The immunogenic antigen or immunogen

Like infectious sub-unit vaccines, AD vaccines contain i) an immunogen(s), which determine the specificity of the immune response, and ii) an adjuvant or immune modulator that affects the stimulated immune response, i.e., Th1 vs. Th2, regardless of the protein immunogen (Marciani, 2003); but, there are also divergences between these vaccines. While infectious disease vaccine immunogens are "static", i.e., the neutralizing epitopes are physically stable and do not change with time except by mutations (Naz and Dabir, 2007); the known protein immunogens for AD vaccines, e.g., amyloid-β (Aβ), tau protein and α-synuclein, are in a constant flux due to oligomerization, post-translational modifications, and/or conformational changes (Hoozemans et al., 2006). Indeed, the physical processes leading to the formation of conformational epitopes unrelated to the antigen's amino acid sequence, are a unique characteristic of the amyloid-forming proteins (O'Nuallain and Wetzel, 2002; Ladiwala et al., 2012). Hence, while it is feasible to use in infectious disease vaccine immunogens carrying only the neutralizing epitopes, it is unlikely that in AD vaccines partial immunogens would induce the formation of the many antibodies needed to target the various forms of those proteins involved in the disease process. In fact, the use of shortened antigens as immunogens was implemented to avoid the damaging pro-inflammatory Th1 immune response elicited by the AN1792 AD vaccine, which contained $A\beta_{1-42}$ with T-cell epitopes plus the potent Th1 adjuvant QS-21 (Wisniewski and Konietzko, 2008). Although 6% of the patients immunized with the AN1792 AD vaccine developed acute meningoencephalitis, it is probably that any additional immunizations would have increased that percentage. Also, it should be emphasized that the inflammatory response was initiated by the adjuvant not the antigen. Yet, that in the mouse model the vaccine having $A\beta_{1-42}$ plus QS-21 yielded promising results without side effects, underlines the differences in response between species.

Though the AD vaccine development has been focused largely on Aβ, there is evidence that the tau protein, sometimes in conjunction with Aβ, plays an important role in AD pathology (LaFerla, 2010; Ittner et al., 2010; Bolmont et al., 2007). Indeed, soluble Aβ dimers isolated from the brains of late-onset AD patients induce tau hyperphosphorylation as well as neuritic degeneration (Jin et al., 2011); a situation that shows the intimate relationship between these proteins present in the neural cells. Hence, as it has been proposed, an option would be to immunize with various relevant antigens rather than single ones (Golde et al., 2010; Lambracht-Washington and Rosenberg, 2013; Wisniewski and Boutajangout, 2010), i.e., to use polyvalent vaccines. Considering the potential for cooperative damaging effects of proteins like Aβ, tau protein and α-synuclein in AD, the multi-target vaccination approach is sound. However, increasing the number of antigens could result in an increase in the risk of developing damaging inflammatory immunoresponses. This situation highlights the critical need for vaccines that prevent damaging Th1 while inducing a protective Th2 immunity.

A potential advantage of passive and presumably active immunotherapy is that from the aducanumab clinical results, these therapeutic approaches apparently are not hindered by genetic factors. Indeed, passive immunotherapy performed equally well in patients with and without known genetic risk factors like *APOE ε4* (Keller, 2015; Jeffrey, 2015). A reassuring observation, as supports the development of a "generic" vaccine(s) with well-defined immunogens that may be widely used without genetic limitations.

2.1.1. Shortened or partial immunogens

In proteinopathies, the selection between whole or partial antigens as immunogens could be intricate, as the immunogens are normal proteins that become pathogenic due to misfolding and aggregation (Hoozemans et al., 2006). For instance, in immunogens where oligomerization and/or conformation produce epitopes significant for immune protection, like Aβ, the choice needs be the whole antigen (Dalgediene et al., 2013; Brorsson et al., 2010; Vasilevko et al., 2010). But, in immunogens like tau the situation is more complex because of the occurrence of oligomerization and post translation modifications, like hyperphosphorylation, which causes local changes relevant for AD pathology that can respond to immunotherapy (Huang and Jiang, 2009; Schneider et al., 2004; Ubhi and Masliah, 2011). However, several studies have shown that oligomeric non-phosphorylated tau is an effective immunotherapeutic target, regardless of its state of phosphorylation, a