ARC Journal of Immunology and Vaccines
Volume 2, Issue 1, 2017, PP 9-15
www.arcjournals.org

Progress in Immunotherapy for Alzheimer's disease-How to Overcome Recently Found Obstacles

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Abstract: *Twenty years have passed since Schenk et al. developed peptide vaccines for Alzheimer's disease (AD). However, subsequent clinical trials with active and passive immunization have failed to obtain sufficient outcomes to halt or improve cognitive decline. Other non-immunological therapies have also been unsuccessful in achieving satisfactory results. In this review article, we analyze factors regulating the results of these outcomes and look for ways in overcoming them. We also introduce recently developed DNA vaccines that targets both Aβ and tau deposits.*

Keywords: *Alzheimer's disease (AD), amyloid β (Aβ), tau, immunotherapy, DNA vaccine*

1. Introduction

Alzheimer's disease (AD) is the most common cause of age-related dementia. The disease affects more than 12 million people worldwide and is characterized by progressive memory impairment and cognitive decline [1]. Senile plaques (Aβ deposition) and neurofibrillary tangles (hyperphosphorylated tau deposition) are two major hallmarks of AD pathology. Both Aβ and tau are neurotoxic and work independently or in combination to progress the disease. Based on the accumulated knowledge, investigators and clinicians have tried to develop immunotherapies for AD for the past two decades. As a result, active (peptide vaccines) and passive (monoclonal antibodies, mAbs) immunization against Aβ have been developed, and some have been used in clinical trials. However, at present, neither vaccines nor mAbs have showed satisfactory results. Although anti-Aβ vaccination was able to significantly reduce Aβ deposits in the brain of AD patients, no beneficial effects were observed with regards to cognitive decline. The status of various clinical trials is listed in Table 1 (cited from Ref [2] with permission).

In this article, we will briefly summarize the history of immunotherapy, analyze its obstable and then discuss the possibility for new immunotherapies.

2. Amyloid Cascade Hypothesis (ACH)

The theoretical background for immunotherapy is mainly based on the amyloid cascade theory (ACH). However, initial clinical trials using Aβ peptide vaccines (AN1792) raised doubt concerning this theory. Holmes et al. [3] reported that the autopsy of some AD patients who received the AN1792 vaccination had near complete depletion of Aβ deposits in the brain; however, these patients did not show any improvements in cognitive decline. These findings suggested that Aβ deposition is not a main player in AD pathogenesis. Despite this criticism, the accumulated evidence strongly suggests that Aβ deposition is an important prerequisite for the development of AD, which have been shown in clinical and experimental settings [4, 5]. Ittner et al. demonstrated that enhanced redistribution of hyperphosphorylated tau from axons to the somatodendritic compartment during AD pathogenesis may increase tau-dependent sorting of Fyn to the dendrites, which results in the boosting of excitotoxic signaling and increase in the toxic effects of Aβ on neurons [6]. This group of proteins has been termed "Fyn-tau-amyloid toxic triad" [7]. Recent progress in ACH is well summarized in a review article [8].

3. Immunotherapy Targeting Aβ

In 1999, Schenk et al. demonstrated that monthly inoculation with a synthetic Aβ peptide vaccine could lead to high anti-Aβ antibody titers and dramatic reductions of Aβ deposition

in PDAPP transgenic mice [9]. Subsequent studies demonstrated that clearance of Aβ deposits following immunization protected APP - transgenic (Tg) mice from developing memory deficits[10,11]. When developing antibody - mediated immunotherapy either using vaccines or mAbs, it is important to determine whether the antibody targets intra- or extracellular components of neuronal cells; however, only few antibodies are known to penetrate the cell membrane and function intracellularly. Recently, it was demonstrated that Aβ [12, 13] and tau [14] play a prion-like role in the formation of AD pathology. Certain types of Aβ and tau, such as pyroglutamate Aβ (AβpE3-42) and hyperphosphorylated tau, induce the misfolding and aggregation of normal proteins. These results suggest that antibodies that function against extracellular targets can be developed against these molecules. Recent findings regarding prions are summarized by Collinge [15].

4. PASSIVE IMMUNIZATION

Immunotherapies have become focused on passive immunization using mAbs after the clinical trials with the anti-Aβ vaccine, AN1792, were stopped due to the development of meningoencephalitis in some treated patients. Recent clinical trials for active and passive immunizations are listed in Table 1 (cited from Ref.[2] with permission). Although bapineuzumab, solanezumab and other mAbs were employed in clinical trials to treat mild to moderate AD, none of them showed satisfactory results [16-18]. Based on these results, mAbs were subsequently used in prevention trials such as DIAN, A4 [19] and API [20] (Table 1). However, currently, there are no reports suggesting the marked preventive effects of mAb treatment. Furthermore, Eli Lilly abandoned solanezumab as treatment for mild dementia [21]. Very recently, it was reported that aducanumab, an mAb which selectively targets the aggregated Aβ, reduced Aβ plaques and slowed cognitive decline in phase I clinical trials [22]. However, it remains to be undetermined whether this treatment is effective in improving cognitive decline [23]. Furthermore, evidence that aducanumab is superior to previous mAbs, such as bapineuzumab and solanezumab, is not available at the present time.

Table1. *Cited from Ref [2] with permission. Aducanumab is not listed. See text for details.*

Table 1
Current status of selected anti-Alzheimer's drugs in clinical trials.

Drug	Mechanism of action	Clinical stage	Status
AN-1792	Anti-Aβ vaccine	Phase II	Discontinued
CAD106	Anti-Aβ vaccine	Phase II	Terminated
ACC-001	Anti-Aβ vaccine	Phase II	Terminated
Bapineuzumab	Humanized monoclonal anti-Aβ antibody	Phase III	Discontinued
Solanezumab	Humanized monoclonal anti-Aβ antibody	Phase III and II/III	Ongoing
Gantenerumab	Humanized monoclonal anti-Aβ antibody	Phase II/III	Ongoing
Crenezumab	Humanized monoclonal anti-Aβ antibody	Phase II	Ongoing
IVIG	Human polyclonal anti-Aβ antibody	Phase III	Ongoing
GSK933776	Humanized monoclonal anti-Aβ antibody	Phase I	Terminated
BAN-21	Humanized monoclonal anti-Aβ antibody	Phase I/II	Ongoing
AADvac1	Anti-tau vaccine	Phase I	Ongoing
ACI-35	Anti-tau vaccine	Phase I	Ongoing
Semagacestat	γ-Secretase inhibitor	Phase III	Discontinued
Avagacestat	γ-Secretase modulator	Phase II	Discontinued
Begacestat	γ-Secretase modulator	Phase I	Terminated
NIC5-15	γ-Secretase modulator	Phase II	Ongoing
CHF-5074	γ-Secretase modulator	Phase II	Terminated
MK-8931	β-Secretase inhibitor	Phase II/III	Ongoing
LY2886721	β-Secretase inhibitor	Phase II	Discontinued
AZD 3293	β-Secretase inhibitor	Phase II/III	Ongoing
LY3314814	β-Secretase inhibitor	Phase II/III	Ongoing
E2609	β-Secretase inhibitor	Phase II/III	Ongoing
Tideglusib	GSK-3β inhibitor	Phase II	Terminated
Intranasal Humulin R	GSK-3β inhibitor	Phase II	Ongoing
Intranasal glulizine	GSK-3β inhibitor	Phase II	Terminated
Idalopirdine with donepezil	5-HT_6 receptor antagonist	Phase III	Ongoing
SB742457 with donepezil	5-HT_6 receptor antagonist	Phase II	Terminated
ABT-288	H_3 receptor antagonist	Phase II	Terminated
GSK239512	H_3 receptor antagonist	Phase II	Terminated
Azeliragon	RAGE inhibitor	Phase III	Ongoing
Encenicline	α7-nAChR inhibitor	Phase III	Ongoing
Nivaldipine	Calcium antagonist	Phase III	Ongoing

These results raise at least two possibilities. First, targeting only Aβ may not be sufficient enough to halt or improve cognitive decline; this will be discussed in detail below. The second relates to the antigen specificity of mAbs. Furthermore, it is unlikely that the stage of AD is important when starting treatment since the prevention study did not show favorable outcomes.

There is little known concerning the antigen specificity of anti-Aβ mAbs, which were used in clinical trials. The linear sequence recognized by each mAb is known, but it is still unclear whether or not mAbs recognize conformational

epitope(s) of various Aβ species. Bapineuzumab, solanezumab, gantenerumab and crenezumab have been reported to bind Aβ monomers, oligomers and fibrils; however, most mAbs were unable to achieve beneficial effects in clinical trials [24]. We have done an extensive survey of the literature and found only one paper regarding this topic. Watt et al. examined the binding ability of clinically used anti-Aβ mAbs and found that bapineuzumab, but not solanezumab and crenezumab, demonstrated target engagement of brain Aβ [25]. This result, however, was heavily criticized by Holzman's group in terms of the techniques that were used [26]. Thus, further investigations are required to determine the degree of specificity of these mAbs. Unfortunately, bapineuzumab and solanezumab did not reach satisfactory endpoints in clinical trials, and their developments have been discontinued.

5. ACTIVE IMMUNIZATION

5.1. AN1792

Active immunotherapy seems to be more effective in reducing the Aβ species compared with passive immunotherapy. Several autopsy reports demonstrated that some Aβ vaccine (AN1792)-treated patients showed complete disappearance of Aβ plaques [3, 27, 28]. Furthermore, AN1792 vaccination induced anti bodies against a wide variety of Aβ species [29]. As mentioned previously, the AN1792 treatment did not stop the progression of cognitive decline [3]. Boche et al. reasoned that the failure to halt cognitive decline by the AN1792 vaccine was due to its limitations in reducing aggregated tau in the neuronal process [28]. These results raise the possibility that Aβ depletion alone is not sufficient to halt cognitive decline.

5.2. CAD106

CAD106 is a peptide vaccine comprising of Aβ1-6 coupling to the virus-like particle Oβ [30, 31]. Phase 2/3 trials began in November 2015 and are set to continue until 2023 with a 5-year treatment period. This study aims to enroll 1,340 homozygous ApoE4 carriers between the ages of 60 and 75 who are cognitively normal (Alzforum, CAD106). Therefore, conclusions made at a future date will determine whether CAD106 is effective in improving or halting cognitive decline.

6. ANTI-TAU IMMUNOTHERAPY

Failure of the anti-Aβ immunotherapies in clinical trials, especially those using mAbs, prompted the development of anti-tau immunotherapy. Recent progress in this area is well summarized in review articles [32, 33]. Both AADvac1 [34] and ACI-35 [35] are peptide vaccines and are currently in clinical trials. However, it is still early to evaluate the effects of these drugs. There is particular interest in determining whether anti-tau immunotherapy is effective for patients with early to moderate AD. As mentioned previously, anti-Aβ immunotherapy did not show satisfactory results at this stage of the disease. Furthermore, the tau sequence employed for immunotherapy seems to be important. In the experimental setting, Umeda et al. demonstrated that using several anti-tau mAbs, the anti-pSer413 antibody, but not the anti-pSer396 antibody, was effective in reducing tau deposits and improving memory [36]. Very recently, it was reported that tau immunotherapy inhibits not only tau but also Aβ pathology [37, 38]. Since the effects of anti-Aβ immunotherapy on tau pathology is very limited [39, 40], it is possible that anti-tau therapy provides more benefits than anti-Aβ therapy. Although beneficial effects such memory improvements in mice models are important, it does not guarantee the effectiveness of anti-tau vaccines and mAbs in clinical trials as experienced in the anti-Aβ immunotherapies.

7. ANTI-Aβ (YM3711 [41]) AND ANTI-Aβ/TAU (YM7555 [42]) DNA VACCINES

To compensate the disadvantage of conventional immunetherapies, DNA vaccination has been developed as a new therapy for AD [43, 44]. At the injection site, the vaccines are taken up by muscle cells and the Aβ peptide-protein complex is produced for a certain period [45]. Translated Aβ or Aβ/tau complex stimulates immune responses in the host, and induced anti-Aβ and/or tau antibodies. Importantly, immune responses of the host can be easily manipulated to obtain a Th2 type reaction [43, 46, 47].

7.1. YM3711 Vaccination Elicits Antibodies against A Broad Spectrum of Aβ Species and Deletes Them from the Brain of AD Mice Models

Aβ oligomers as well as other Aβ species and amyloidogenic peptides are neurotoxic and play a pivotal role in AD pathogenesis [48]. In particular, it is important to remove conformationally abnormal structures through treatment. We attempted to develop new DNA vaccines and found that an IgL-Aβx4-Fc-IL-4

vaccine, designated as YM3711, was found to induce significantly higher levels of antibodies not only against Aβ1-42 but also AD-related molecules including AβpE3-42, Aβ oligomers and Aβ fibrils. Importantly, YM3711 significantly reduced these Aβ species in the brains of mice [48]. Thus, YM3711 is a powerful DNA vaccine targeting a wide range of AD-related molecules and is worth examining in clinical trials. Furthermore, we are attempting to develop more effective vaccines in a subsequent project.

7.2. Design of Aβ/Tau Vaccine (YM7555) and Vaccination Protocol

In order to create more effective immune therapies for AD, we have developed new DNA vaccines that target tau alone or both Aβ and tau depositions[49]. Of these vaccines, YM7555 has four tandem - repeats of human Aβ1 - 42 and human tau 379 - 408 sequences that are connected to both ends of the Fc portion of immunoglobulin.

3x Tg and wild-type mice were injected biweekly with YM7555 at a dose of 100 μg/ injection in mice and 1 mg/injection in rabbits. Titers of anti-Aβ1-42 and anti-tau antibodies were determined by ELISA using plasma taken at the indicated time points.

7.3. Effects of YM7555 Vaccination

3x Tg mice were injected with YM7555 intramuscularly, and the kinetics of anti-Aβ (**Figure 1A-C**) and anti-tau (**Figure 1D-F**) antibody titers were determined by ELISA. The results of individual mice (n = 3) are shown. Both anti–Aβ and anti-tau antibody titers started to increase 4 or 8 weeks after the first vaccination and peaked at 8 or 12 weeks in all vaccinated mice. At the end of the study, anti–Aβ and anti-tau antibodies showed approximately a 10-fold increase. The results of the three studies are summarized in **Figure 2**. YM7555 immunization induced moderate (500-1000%) to high (>1000%) titers of anti-Aβ antibodies. Interestingly, the same YM7555 vaccination induced high titers of anti-tau antibodies in 3 x Tg mice. From these results, it is clear that the administration of the Aβ/tau vaccine (YM7555) induces a significant increase in antibodies against Aβ and tau (**Figure 2**) [49].

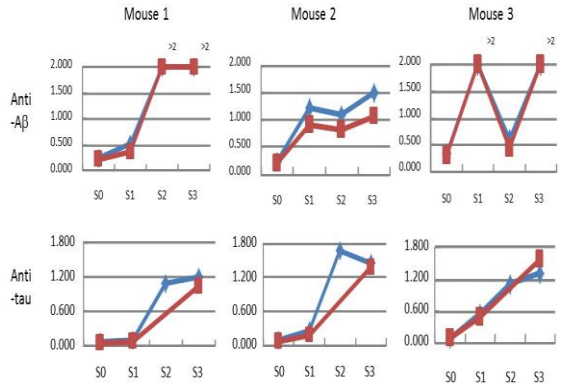

Figure1. Induction of anti-Aβ1-42 (upper panels) and anti-tau (lower panels) antibodies with an Aβ/tau vaccine (YM7555). *3x Tg mice were injected with YM7555 intramuscularly according to the protocol described in the text. The kinetics of anti-Aβ and anti-tau antibody titers of individual mice are shown. The blue and red line represents x16- and x32-diluted plasma, respectively. Transient decrease of the anti-Aβ1-42 antibody titer in the S2 plasma (right upper panel) is most likely a technical error since it is unlikely that the decrease in antibodies occurs for such a short duration.*

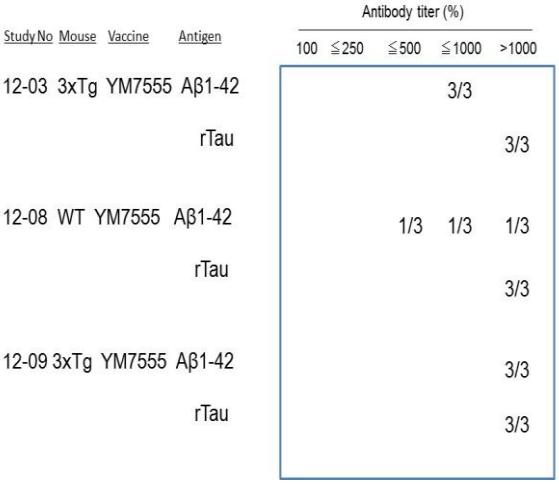

Figure2. Summary of anti-Aβ1-42 and anti-tau antibodies in mice. *Percent increase of the indicated antibodies were categorized into 5 groups (≦100%, ≦ 250%, ≦ 500%, ≦ 1000% and >1000%). Pre-immune plasma was assigned a percent value of 100. The numbers of mice per total number (n = 3 for each group) in the indicated category are shown.*

To assess the Aβ and tau reduction efficiency of Aβ/tau vaccines, 3x Tg mice were administered with YM7555 [49]. After repeated vaccinations, the levels of Aβ and tau in the cerebral cortex were quantified by sandwich ELISA. As shown in **Figure 3**, the amount of Aβ (panel A), total tau (panel B) and phosphorylated tau (panel C) was lower than untreated Tg mice. Importantly, phosphorylated tau, which is neurotoxic, was no longer detected after YM7555 vaccination (panel C) [49].

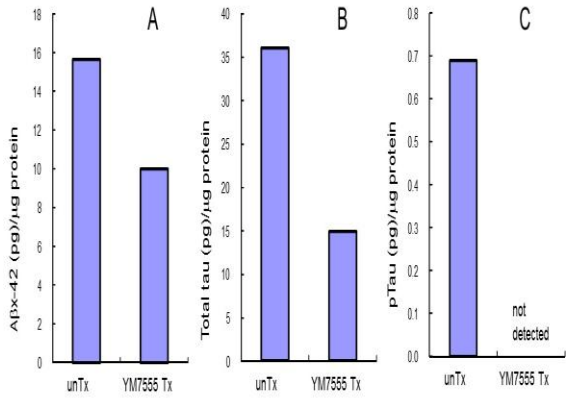

Figure3. Quantification of Aβ, total tau and phosphorylated tau in the brain by sandwich ELISA. *Sandwich ELISA showed that the amount of Aβ deposits in the frontal cortex decreased in the vaccinated mice (right bar in Panel A) compared with the untreated age-matched Tg mice (left bar in Panel A). Similar analysis showed that the amount of total tau (B) and phosphorylated tau (C) in the vaccinated mice decreased compared with the untreated age-matched Tg mice (left bars in Panels B and C).*

8. Discussion and Conclusion

Failures in improving cognitive decline by peptide vaccine (AN1792) and several anti-Aβ mAbs in clinical trials raised the possibility that these therapies are ineffective for patients with mild to moderate AD due to the late start in treatment. This prompted the anti-Aβ prevention trial for clinically normal individuals with a genetic predisposition for AD or who carry severe risk factors. Unfortunately, the prevention trials also showed unfavorable results, which strongly suggested that targeting only Aβ is not sufficient to obtain beneficial effects. The point is that Aβ reduction by the treatment showed little beneficial effects on tau pathology, thereby anti-Aβ immunotherapy did not halt cognitive decline in AD patients. Very recently, the A4 (the Anti-Amyloid treatment in Asymptomatic Alzheimer's study) researchers are trying to overcome this obstacle by raising the solanezumab dosage (Alzform, June 29; 2017). It seems to be too optimistic to anticipate that this modification would be effective in prevention of AD development. As mentioned earlier, some species of Aβ and tau are neurotoxic alone or in combination. Taken all the situations into consideration, it is the time to start immunotherapy targeting both Aβ and tau. Although these studies are currently very preliminary, more focus should be given to vaccine projects that target Aβ and tau.

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Citation: *Yoh Matsumoto, Kuniko Kohyama. Progress in Immunotherapy for Alzheimer's disease-How to Overcome Recently Found Obstacles, ARC Journal of Immunology and Vaccines. 2017; 2(1):9-15.*