Immunotherapies for Alzheimer's Disease

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Abstract. Alzheimer's disease (AD) is the main cause of dementia and it is a neurodegeneration disease. Numerous evidence has shown that amyloid β (Aβ) and tau protein are two main "triggers" of this disease. The Aβ has been main target for decades, and this review will discuss both active anti-Aβ and passive anti-Aβ immunotherapies. Recently, the tau protein has emerged as a new leading target for AD treatment. Several active and passive anti-tau antibodies will also be discussed in this review. Finally, it provides some suggestions about the future strategies to overcome AD.

Keywords: Immunotherapies · Alzheimer · Anti-amyloid · Tau

1 Introduction

Alzheimer's disease (AD) is the leading cause of dementia and one of the big health challenges worldwide [1]. It is a neurodegenerative disease that could induce age-associated cognitive reduction [2]. A growing body of evidence indicated that the Aβ-protein and the tau protein play vital roles in AD [2]. Under normal conditions, the most common species in human brain is peptide Aβ40 and this peptide is soluble. However, in the brain of AD patients, this normal peptide changes to a toxic form, Aβ42, and accumulates around the neurons. Basically, the deposition of Aβ42 is abnormal and forms extracellular plaques [3]. In terms of tau protein, it is a normal substance within cells, and its main function is to help maintain the stability of cell structure. In neurons, this protein offers supports for axon structure and enhances the transfer of intracellular compounds and organelles [4]. Nonetheless, there are multiple approaches for tau protein change to a pathological state. Posttranslational modification (e.g., hyperphosphorylation, acetylation and nitration) is a method that could change the function of tau protein from beneficial to harmful [5]. Hence, the Aβ and tau proteins become two main targets for developing antibodies to treat AD patients. In this review, both anti-amyloid immunotherapies and anti-tau immunotherapies will be discussed.

2 Anti-amyloid Immunotherapies

Immunotherapy is traditionally divided into active vaccine method and passive vaccine method. Active immunotherapy is injected a vaccine which is a compound of Aβ peptide with adjuvant to influence the immune system [6]. To test the safety of human

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immunogenic accumulation of Aβ peptide immunization, researchers randomized AD patients from mild to modulate into control placebo group and treatment group in 2000. The result of this experiment showed that there was no significant difference between control group and treatment group [7]. Additionally, the short-term clinical efficiency of plaque clearance was not obvious [7]. After two years, the clearance of Aβ was obvious in the treatment group, but around 6 percents of patients in the treatment group suffered meningoencephalitis after injected the trial vaccine. This result made the vaccine trail stopped [7]. The cause of meningoencephalitis from this test vaccine remained uncertain, however, the possible reason may be the Th1 adjuvant penetrated into the central nervous system and was recognized by the Aβ-specific T cells, leading to autoimmune neuritis [8]. Another possible reason may be polysorbate 80 used in the vaccine [8]. Recently, the new active vaccine has been applied to reduce the Th1 cellular immune response [9]. CAD106 is a novel active immunotherapy that is designed for reduce Aβ without Aβ-specific T cell response. Winblad and colleagues have conducted this new vaccine for both mild and moderate AD patients, the result illustrated that the CAD106 had an acceptable antibody response in patients [9]. Although the CAD106 trial did not induct any meningitis, it still exhibited some side effects, involving nasopharyngeal response and injection site response [9].

Meanwhile, the failure of active vaccination lead to numerous of efforts in passive immunotherapy. Typically, passive immunotherapy refers to the direct employ of anti-Aβ monoclonal antibody [10]. Some antibodies have showed success in pre-clinical trials and have been tested in clinical trials. Bapineuzumab is the first generation of anti-amyloid-beta monoclonal antibody that can recognize the N-terminal domain of Aβ. A double-blind, randomized Bapineuzumab experiment divided patients with mild and moderate AD into placebo-control group and treatment group. Despite the bapineuzumab was demonstrated the ability to bind all forms (fibrillar, oligomeric, and monomeric) of Aβ and decrease the amount of Aβ in preclinical trial, the result showed that there was no significant cognitive improvement in either group, and both companied with amyloid relevant edema [11]. Solanezumab is another antibody that is designed for reducing the intermediate position of Aβ. The phase II clinical trial has demonstrated its safe and effective profile in decreasing the amyloid plaque, and the cognitive ability of AD patients has been promoted [12]. For other antibodies, the first fully human monoclonal antibody for Aβ is Gantenerumab, it is designed to combine the amyloid plaques and eliminate them. Gantenerumab differs from bapineuzumab and solanezumab in that it notices both the N-terminal and central domain of Aβ. The phase I clinical trial of gantenerumab exhibited an acceptable efficacy of removing Aβ, but there was no data about its efficacy for cognitive effect [14]. The phase II trial is still ongoing [13]. Ponezumab is also a humanized monoclonal antibody that aims to decrease T-cell response. The preclinical test has proven the safety of this compound and the first phase of clinical trial has completed [14]. The result of phase I trial illustrated that ponezumab is a compound with well tolerated profile and has no serious adverse effects [14]. But it also demonstrated some side effects, such as mild to moderate headache, back pain and upper respiratory tract infection [14].

Table 1. Ongoing anti-tau therapy project

Antibody program	Antibody	Species	Epitope	IP
ACImmune, Janssen, KU Leuven, and Fred van Leuven	ACI-35	Active vaccine	pS396/pS404 peptide liposome formulation	WO2010115843
ACImmune, Genentech, KU Leuven, and Fred van Leuven	hACI-36-2B6-Ab1 and hACI-36-3A8-Ab1	Humanized mouse monoclonal	pS409	WO2013151762
Axon Neuroscience and Michal Novak	AADvac1	Active vaccine	294–305 peptide ^{294}KDNIKHVPGGGS^{305}	WO02062851
	DC8E8	Humanized antibody	Generated from immunizations with 294–305 peptide	WO02062851
Biogen Idec, Panima Pharmaceuticals AG, and Roger Nitsch	NI-105.4E4, 24B2, and 4A3	Human autoantibodies	V339, E342, D387, E391, K395	WO2012049570; US2012087861
C_2N Diagnostics, David Holtzman, and Marc Diamond	HJ9.3, HJ9.4, and HJ8.5	Mouse monoclonal	306–320, 7–13, and 25–30	
Eli Lilly and Peter Davies	PHF1, MC1	Mouse monoclonal	pS396/pS404, conformational	WO9620218
Hoffman-La Roche	2.10.2, 2.20.4, and 5.6.11 MAb86	Rabbit monoclonal	pS422	WO2010142423
iPerian/BMS	IPN001, IPN002, IPN007	Humanized mouse monoclonal	9–18	US2014294831
Intellect Neurosciences Inc. and Lester Binder	TOC-1 and TauC3	Mouse monoclonal	Tau-dimers and caspase-cleaved Tau421	US8697076 US2012244174
Lundbeck, NYU, and Einar Sigurdsson	4E6, 6B2, and scFv235	Mouse monoclonal	pS396/pS404, total tau, other hyperphosphorylation, conformational, and truncation sites	US2008050383 US2010316564
Pfizer		Chicken monoclonal	pT212/pS214, pT231/pS235, and pS396/pS404	WO2014016737
Prothena Corporation, Lars Ittner, and Jürgen Götz	pS404-Ab1/Ab2 pan-Tau	Mouse monoclonal	pS404 and total tau	WO2014134685
Prothena Corporation	h16B5	Humanized mouse monoclonal	23–46 peptide	WO2014165271
Teijin Pharma Ltd and Hitoshi Mori	Ta1505	Mouse monoclonal	pSer413	WO2013180238

3 Tau Immunotherapy

Aβ has been main target of immunotherapy for over ten years, but due to the anti-Aβ immunotherapies having limited success in treating AD patients, the target has been changed to tau. This has given rise to anti-tau immunotherapies and these therapies became popular in clinics [15]. The hypothesis of anti-tau immunotherapy is that the antibody will reach the brain then bind with extracellular and/or intercellular pathological tau species, which could lead to clearance of these tau species [16]. Recent tau-based immunotherapies in clinical trials are summarized in Table 1, the detail of some vaccines will be discussed below.

One of the active immunotherapy of tau is ACI-35, it is a vaccine that has been supported by the animal test. In the wide type and transgenic P301L mice, this vaccine induced a fast immune response, which leaded to a mild decrease in tau pathology. In addition, this positive effect did not show any relevance with adverse inflammation response [17]. However, the clinical trial for ACI-35 is lack of details now. In comparison, AADvac1 was the first clinical trial of active tau immunotherapy with detailed data. It is a compound that contains a tau294-305 peptide and N-terminal cysteine fragment in order to bind the peptide with the surface of the keyhole limpet haemocyanin (KLH) protein, and its adjuvant is Alhydrogel alum. The results of this study demonstrated that no adverse effects had been reported through multiple detection methods, such as blood biochemistry analysis, urinalysis and cardiorespiratory safety pharmacology [18]. Regarding its preclinical study, AADvac1 has been released as a vaccine in clinical trials

by Axon Neuroscience SE. Since it was only tested in phase I clinical trail, results are inconclusive and has not been released on US National Library of Medicine database [19].

Several passive tau immunotherapies are also recently in early development phases for AD patients. For example, the AC immune and Genentech is detecting a mouse monoclonal antibody to resist tau409, but the data is limited. Axon neuroscience is also detecting antibodies that can recognize and clear tangle inducing residues [20], who find that antibody DC8E8 seems to be qualified in transgenic rats, and this antibody has been humanized [21]. A group at University Zurich developed a new strategy to create anti-tau antibody [16]. They directly isolated autoantibodies of tau in healthy elderly individuals without degeneration of tau-pathology to acquire antibodies instead of obtaining antibodies from transgenic mouse [16]. Several antibodies have been isolated using full-length recombinant human tau (2N4R) as "bait" to retrieve tau-specific antibodies [16]. MAb86, another antibody, designed by the Roche group that aims to recognize the pS422 epitope of tau, which is located at dendrites of neuron [22]. Apart from those antibodies have mentioned above, there are many other groups are detecting passive anti-tau immunotherapies for AD patients, such as iPerian Inc. Developed antibodies IPN001 and IPN002, which are mainly used to recognize N-terminal fragments [16].

4 Discussion

Basically, both anti-Aβ immunotherapies and anti-tau immunotherapies exhibited some clinical efficacy for the treatment of AD. Some evidence demonstrated that there is a stronger association between cognitive disorder and tau protein deposition than with Aβ accumulation [23]. Additionally, the tau protein presents a very low level in extracellular area, in other words, the lack of general microglial activation would **increase** hemorrhage and edema and that have been observed in anti-Aβ immunotherapies in animals and humans [24]. Therefore, the burgeoning effort has been focused on anti-tau therapies recently. For the future direction, multiple evidences have shown that the oligomers of tau seem to be the most toxic forms of this protein, and the next generation of antibodies needs to be focused on oligomers [25]. However, the connection between cognitive disorder and tau protein deposition is still not fully understood [26]. Hence, the mechanism of Aβ and tau proteins should be detected in further studies.

Despite numerous immunotherapies have been developed or are ongoing, there is still a lack of efficient treatment to cure AD. With the purpose of finding out the long-term clinical efficacy and safety of these immunotherapies, certain issues still need to be resolved. For example, both active immunisation and passive immunisation antibodies should improve their abilities to cross blood brain barrier. In fact, only very small percentage of antibodies enter the brain successfully (~0.1%) [8]. In clinical trial, every antibody needs to be treated with caution, especially for active vaccines. Since it may induce the immunosenescence and autoimmune response which can lead the antibody against normal proteins. Furthermore, early screening of high-risk population should be promoted, as the current available immunotherapies are concentrated on clearing

plaques and tangles after the symptoms onset. For instance, using the positron emission tomography (PET) scan and spinal fluid analysis would indicate individuals with amyloid accumulation before high degree of neural damage has taken place [27].

5 Conclusion

In this review, both anti-Aβ and anti-tau immunotherapies have been discussed. The active and passive anti-Aβ therapies have been the main targets to cure AD, but the clinical efficacy is limited. In the past decades, the anti-tau therapies have been the new leading targets for treating AD. Many active and passive anti-tau programs are ongoing and the results of animal tests are promising. Some of them have finished the first clinical trial (e.g., AADvac1), but the available data for long-term clinical safety and efficacy still remains limited. In fact, both active and passive immunotherapies have certain issues that need to be addressed, such as improve the ratio of antibodies passing the blood brain barrier and entering the human brain successfully. In the future, binding the anti-Aβ therapies and anti-tau therapies may be the possible way to finally overcome AD.

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