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TAU IMMUNOTHERAPY FOR ALZHEIMER'S (Review Article)

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Abstract

Alzheimer's is a tormenting disease that progressively destroys a person's cognition. Researchers have toiled long and hard to find a cure or slow the course of this disease. Therapies have mainly targeted the two hallmarks of Alzheimer's pathophysiology: amyloid and tau protein. This paper sheds light on the new developments in the field of immunotherapy aimed against tau protein, particularly in comparison to the thus far futile efforts of targeting amyloid. Tau targeting immunotherapy is emerging as a promising therapeutic option.

Introduction

Several advances made by medical science have resulted in the increase of life expectancy. Owing to this, diseases affecting the aging population cropped up. One of the most devastating is Alzheimer's, emerging as the fifth leading cause of death in people over 65 years of age. Without any progress in the prevention, slowing down or curing of this disease, Alzheimer's will affect more than 13.8 million people by 2050 [1].

A thorough understanding of the pathophysiology of Alzheimer's is required before exploring its therapeutic options. Formation of beta amyloid plaques and neurofibrillary tangles by tau protein are the pathophysiologic hallmarks of this disease [2]. Cleavage of amyloid precursor protein (APP) by an enzyme called "Beta secretase" is responsible for the change in configuration that promotes aggregation [3].

Meanwhile, tau protein naturally functions as a microtubule stabilizer. Upon hyperphosphorylation they are rendered incapable of normal and appropriate function. They aggregate to form oligomers or paired helical filaments, the latter of which is more prominent in Alzheimer's.

Currently there are no effective disease modifying drugs to treat Alzheimer's. Anticholinesterase inhibitors (e.g. donepezil, rivastigmine and galantamine) along with memantine, a glutamate receptor antagonist, are typically used for symptomatic care but do little to prevent the fundamental pathology, namely that amyloid accumulates extracellularly and tau tangles intracellularly. The logical target for initial treatment options is prevention of these processes; amyloid was first targeted [1]. However, these efforts have not been very fruitful. Further research showed that altered Tau function and morphology preceded the clinically evident onset of Alzheimers and that Tau neurofibrillary tangles correlated better with the severity of Alzheimer's [4]. Hence there was a shift in focus to Tau targeting therapies, with an up and coming field being immunotherapy targeting Tau protein. If proven to be successful it can be used as a preventive tool to strike before the detrimental effects of this disease sets in.

Why not amyloid?

The role of β-amyloid in the pathogenesis of Alzheimer's disease has been well known for the past 30 years and, until recently, it has been an attractive therapeutic target [3]. What is well documented is that β-amyloid accumulates through alternate cleaving of amyloid precursor protein (APP), and that increased levels of β-amyloid are associated with the beginning and progression of Alzheimer's. Though It is still unknown whether it triggers cell-surface receptors or binds intracellularly, or whether it triggers nothing at all and simply accumulates. Perhaps even more intriguing is that lowering β-amyloid levels do not necessarily improve cognitive function [5, 6]. This in itself suggests that β-amyloid may not be the end-all be-all of Alzheimer's disease.

There are several prevailing therapeutic approaches currently under study. One employs anti-β-amyloid antibodies, the aim being to bind and remove β-amyloid, thus preventing it from exerting its effects. This strategy looks attractive since it precludes any of its pathologic effects. However, clinical trials have not shown any difference in outcome measures. Bapineuzumab was halted in its Phase III trial because it failed to show any effect, and solanezumab also revealed no effect in two of its Phase III trials [6].A second approach involves blockade of β-site APP cleaving enzyme 1 (BACE1). Blockade of the

abnormal cleavage of APP would result in less β-amyloid accumulation. Studies in humans have thus far failed to show any meaningful results, although animal studies are promising.

Other mechanisms of interest are antagonism of receptors that are triggered by β-amyloid and management of risk factors that may accelerate β-amyloid formation.

Until β-amyloid's pathways and mechanisms of disease have been further mapped out, the design and use of therapeutics will likely continue to yield minimal results. Meanwhile, the rise in research surrounding tau protein, another downstream player in Alzheimer's, is perhaps easier and simpler to target. Early results have shown promising safety results, and trials are still ongoing.

Current Tau-Targeting Therapies and Vaccines: Active

Historically, vaccines have saved innumerable lives from infectious diseases. Unconventional vaccines have recently emerged which deals with creating vaccines for non-communicable diseases. Such vaccines work by influencing the immune system to recognize various target proteins and other molecules [7].

Alzheimer's is a disease with a multi-faceted and complex pathology. Due to the failures experienced with therapeutic approaches targeted at amyloid plaques, the focus has shifted to targeting neurofibrillary tangles. Early attempts were made to inhibit kinases or tau aggregation, but these approaches were hampered by the tested drug's toxicity and/or lack of efficacy [8]. Recently, however, the spotlight has fallen on immunotherapy against Tau protein. The most attractive attribute of vaccines is that it can be used as prevention before full fledged Alzheimer's sets in, thereby averting the whole catastrophe. Since the patient's own immune system is producing the antibodies, the emergence of anti-drug antibodies are avoided as well. Additionally, compared to monoclonal antibodies which required repeated dosing and cost a great deal of funds, active immunization with vaccines will have drastically fewer doses and thus is less costly.

However there are a few pitfalls to using active immunization, the most obvious and fearful threat being developing antibodies against normal functioning host protein leading to autoimmune complications. Nonetheless, a few trials have shown vaccines overcoming these challenges and showing efficacy in preventing tau related pathology [9].

Hitherto, two vaccines in particular have had promising results. The first vaccine called AADvac started trials on rats in the year 2013. Researchers found a certain Tau peptide sequence ^{294}KDNIKHVPGGGS^{305} in the regulatory region which was responsible for the oligomerization of tau. This sequence was found with the help of a monoclonal antibody(mAB) DC8E8. Using enzyme linked immunosorbent assay, the Tau domain that bound to this mAB was found. These domains were also found to be discriminatory between pathologic and physiologic Tau [10]. Following its identification, an immunogenic T lymphocyte activating epitope was needed. This was provided in the form of a carrier protein called keyhole limpet haemocyanin protein [11]. The results of this study were positive. Addressing the previously mentioned aspects in vaccine development, AADvac 1 was able to generate high affinity antibodies specifically against pathologic tau in experimentally immunized animals. Additionally the immune response was found to be predominantly of the Th2 phenotype which is a testament to its safety [12].

The vaccine was then introduced for human trials. Patients with MRI- confirmed Alzheimers with an MMSE score of 15-26 were enrolled for the study. Of the 30 people who received six doses of the vaccine, 29 people developed IgG antibody response. When these IgG antibodies were compared for the reactivity to pathologic and physiologic Tau using ELISA, the discrimination between the two forms seemed to be similar to the parental antibody which was using for the sequencing (DC8E8). This confirms that the AADvac vaccine can induce safe, selective, and specific antibody response to pathologic tau. With just 30 participants receiving the drug for a period of 6 months, the sample size and time period were simply not large enough to show any significant cognitive and functional end point. Additionally, the patients continued to deteriorate at the pace of their disease progression. Injection site reaction was the only significant side effect [13]. In the succeeding year another study with the same patients in the phase 1 trial was done as a follow up. This showed that the IgG response was lasting past 6 months since the last vaccination. The decline in cognition was slowed in proportion with the amount of IgG produced,

highlighting the importance of a sound immune system for the success of such a treatment. The next phase of this trial is yet to publish its results [9].

Another vaccine that is worth mentioning is ACI-35. It didn't raise any safety concerns but failed to elicit a robust immune response. Hence it was remade by including another adjuvant to further activate T helper cells. The second version was able to produce a stronger immune response in monkeys and they were specific to phosphorylated Tau. Trials in humans were started in July 2019 and are set to be completed in 2022 (Alzforum.org 2021. ACI-35).

Current Tau-Targeting Therapies and Vaccines: Passive

Given the vital role that tau proteins play in neurons and the neuronal environment, many therapies have been approached to target them. Among the many drugs like small molecule inhibitors, GSK3B inhibitors, microtubule stabilizers, anti-phosphorylation drugs, and tau aggregation inhibitors, immunotherapy has garnered a wide reception owing mainly to its success in animal models due to its varied targetability at early and late-stage diseases and low risk of side effects. The monoclonal antibodies can be made to target various regions and epitopes of the tau protein, including its oligomer or amino acid parts [14]. With the use of active immunization techniques, there has been a concern for immune-mediated long-term side effects due to the body's response [15]. But with passive immunization, it is possible to design monoclonal antibodies against various epitopes of the tau protein and their effects are transient. Another advantage that has been proposed for the use of passive immunization is the ability to individualize the treatment based on a patient's disease severity and specific tau epitopes that can increase the efficacy of the therapy [16]. Currently, there are more passive immunotherapies in clinical trials than active ones, and also apart from their success in-vitro studies and mouse models in disrupting the pathological tau process, many of the currently ongoing trials also show promise in humans.

In healthy individuals the blood-brain barrier limits entry to circulating antibodies to around only 0.1-0.2%. But the reason behind the effectiveness of the antibodies themselves remains largely speculative and various mechanisms have been put forward. While healthy individuals only have around a hundredth of the immunoglobulin reaching the CNS, patients with Alzheimer's disease have a disrupted blood-brain barrier that changes the efficacy of this therapy [17]. There are currently 8 passive vaccines in clinical trials and below are their details.

BIIB092 (Gosurenamab) is a humanized lgG4 monoclonal anti-tau antibody against the N-terminal of fragmented forms of tau that were initially isolated from familial Alzheimer's Disease patients. This monoclonal antibody has already completed phase I studies on patients with progressive supranuclear palsy. There was a dose-dependent accumulation of the antibody in the serum and CSF. Moreover, it has shown to decrease the levels of CSF free tau effectively [18]. Currently this antibody is undergoing phase II trial in patients with mild AD and a positive amyloid PET scan, during which the patients will receive 3 different doses of infusion or a placebo.

ABBV-8E12 (Tilavonemab) is also a humanized IgG4 monoclonal antibody but it targets certain tau amino acids and also an aggregated extracellular version of tau. This antibody has been shown in animal studies to decrease neurofibrillary tangles, impede seeding of tau and also slow down brain atrophy. The drug has been approved for treatment of PSP and currently has completed phase I trials and is undergoing a multi-center randomized placebocontrolled phase II study.

RO6926496, another humanized monoclonal antibody attacks the phosphorylated portion of tau protein. It has been shown that the phosphorylation of tau at certain sites plays a major role in where the tau protein ends up accumulating and what structure it takes [19]. Animal studies that had targeted this epitope of the tau protein have shown decreased levels of tau and an improvement in cognitive assessments. While this antibody had completed the phase I trial, there has been no phase II trial to date.

RO7105705 (Semorinemab) is an anti-tau antibody that was designed for mainly targeting extracellular tau. The presence of the extracellular tau protein has been implicated at various stages of the disease and also a potential driver for inflammation and atrophy [20]. This antibody has completed phase I studies and is currently undergoing two different phase 2 studies. One of the studies targets patients with mild AD or prodromal AD verified by PET or CSF amyloid. The other focuses on patients with moderate AD and who are positive for the tau ligand GTP1 verified through PET.

JNJ-63733657 is a humanized IgG1 anti-tau antibody that targets residue 217 on the tau that is located in the middle region. This is in stark contrast to other antibodies that usually target N-terminal residues [20]. This antibody was reported to reduce pathological tau seeding. After being deemed safe in two phase I trials, this antibody is currently in phase 2 trial on patients with mild AD and a positive PET scan.

BIIB076 is a recombinant human monoclonal anti-tau antibody. This antibody is known to bind to monomeric and pre-formed tau proteins with a very high affinity. This pan-tau antibody is able to block tau aggregation and tau propagation across neurons [21]. After being assessed as safe from animal studies this drug was tested for safety in a phase I clinical trial in healthy volunteers that ended in March 2020.

UCB0107 (Bepranemab) is another humanized IgG4 monoclonal antibody that targets the central region of tau, specifically amino acids 235-246. Again this approach was shown to reduce tau aggregates. This antibody was evaluated for safety on healthy volunteers and in patients with PSP in two separate phase I studies. The phase 2 trial will be underway in 2021.

LY3303560 (Zagotenemab) is a humanized anti-tau antibody that targets a specific conformational epitope of tau in the N-terminal region. It has been shown that it binds with nanomolar affinity to aggregates over monomers [22]. This drug after animal studies has completed two phase I studies and is currently in phase 2.

Table 1: Summary of passive tau-immunotherapeutic drugs in clinical trials

Drug Name	Mechanism	Trial Identifier	Status
BIIB092 (Gosuranemab)	Humanized IgG4 monoclonal anti-tau antibody against N-terminal fragment	NCT03352557	Phase 2, Active
ABBV-8E12 (Tilavonemab)	Humanized IgG4 monoclonal antibody against extracellular aggregated tau	NCT02880956	Phase 2, Active
RO6926496	Humanized monoclonal antibody targeting the tau phosphoepitope pS422	NCT02281786	Phase 1, Completed
RO7105705 (Semorinemab)	Anti-tau humanized IgG4 antibody against N terminus of extracellular tau. Binds all six isoforms of human tau including oligomeric and monomeric forms	NCT02820896	Phase 2, Active
JNJ-63733657	Humanized IgG1 monoclonal antibody that recognizes the microtubule binding region of tau.	NCT04619420	Phase 2, Recruiting
BIIB076	Human recombinant, monoclonal anti-tau IgG1 antibody that targets the mid-domain of the tau protein. Binds to monomeric and fibrillar forms of tau.	NCT03056729	Phase 1, Completed
UCB0107 (Bepranemab)	Humanized, monoclonal IgG4 antibody that binds the central area of tau, between amino acids 235–246 near tau's microtubule-binding domain.	NCT04867616	Phase 2, Not yet recruiting
LY3303560 (Zagotenemab)	Humanized anti-tau antibody that targets a specific conformational epitope of tau (an early pathological form) in the N-terminal region	NCT03518073	Phase 2

Limitations and the Future

As has been shown, Aβ immunotherapy has been largely ineffective to date. Therefore, Tau immunotherapy may be the most prudent course of action, especially once the symptomatic process is

underway. The AN-1792 vaccine seemed to demonstrate some ability to clear Aβ plaque-associated tau lesions by plaque removal in the first successful immunization study, and the anti-Aβ antibody bapineuzumab decreased CSF phospho-tau levels in patients with AD in phase II trials. Unfortunately, these findings did not extend to phase III studies in which bapineuzumab had no effect on tau pathology. These data suggest that any clearance of Aβ during active or passive immunization cannot significantly reduce tau levels to alter the course of the disease, and the next logical step is direct targeting of tau.

Successful tau immunization has shown to reduce tau pathology by targeting single or multiple phospho-epitopes, the amino terminus, full-length, normal and mutant tau. In mice, when given in combination with strong T-helper 1-inducing adjuvants that are not licensed for human use, tau vaccination has been reported to cause toxicity [23]. Due to the occurrence of meningoencephalitis in roughly 6% of the enrolled moderate-to-severe AD patients, the first successful vaccine clinical trial for AD AN-1792 was halted early in 2002 [24]. Although Aβ deposition in the limited number of responders who came to autopsy over the next few years decreased focally in particular brain regions, many were seriously demented at the time of death. Based on in vitro experiments using a monoclonal antibody (DC8E8) which prevents tau oligomerization, the epitope for production of the tau vaccine AADvac1 was selected. Adverse effects were limited to inflammation at the injection site and no deleterious immunological responses were observed during the procedure. To prevent autoimmune-like reactions a large effort was made to test passive immunotherapy using humanized anti-Aβ monoclonal antibodies.

Passive immunization provided a reasonable response to the safety issues arising from active strategies. Patients will not produce their own antibodies and it is possible that the effects of immunization will be transient, thus reducing the possibility of adverse immunological effects. Systemic injection into mice of the Aβ monoclonal antibody specific to the Aβ N-terminus, 3D6 mAb, resulted in the transfer of the antibody to the brain, plaque binding of the antibody, and induction of Fc-receptor-mediated phagocytosis of Aβ deposits [25]. This antibody is the predecessor to Bapineuzumab, a humanized N-terminal-specific mAb, which was later studied in clinical trials in Phase I, II and III. Bapineuzumab has shown no major clinical benefits in 2 large clinical trials in Phase III. Pfeifer et al. has documented increased incidences of cerebral microhemorrhages despite plaque reductions. This has been confirmed by them in other clinical studies in mice. In patients with Alzhiemer's disease those who have one or two Apolipoprotein E ε4 alleles, bapineuzumab treatment has been shown to cause a transient vasogenic edema and microhemorrhage.

In early clinical trials Intravenous immunoglobulin (IVIg) pooled human antibodies showed promise. However, recent studies, including USA's Octapharma Phase II 24-week Octagam 10 percent IVIg study in 58 AD patients showed no major slowing of AD progression [26].

Two new antibodies have been announced for human testing. A phase I clinical trial of JNJ-6373365 passive immunization has been launched by Janssen Pharmaceuticals. The antibody tends to bind to the tau middle region and has been engineered to avoid seeding and spread of tau. UCB0107 is now advancing towards clinical trials. Preclinical research indicated this antibody binds to amino acids 235-246 in the proline rich region of tau and that it was effective in preventing pathological tau spreading. Soon, some other successful tau immunotherapies are expected to enter clinical trials. For example, a large portfolio of anti-tau antibodies is currently being developed by Lundbeck, targeting both total tau and pathological hyperphosphorylated PHF-tau [8].

It is likely that the most powerful antibodies would be those that can attack all pathological tau protein pools, both intracellularly and extracellularly. Finally, it is unclear how closely tau seeding and spread are linked to tau toxicity. An antibody chosen to prevent tau seeding and spread may therefore not inherently block the toxicity of tau.

While the field of AD immunotherapy has developed immensely over the past decade, some problems still remain and will need to be solved in order to see long-term protection and success.

One of the major issues of using active or passive immunization is for the antibodies to cross the blood brain barrier. Usually, only a small amount (roughly 0.1%) of antibodies cross the blood brain barrier, so discovering ways to increase the penetration of antibodies into the brain can be beneficial. The use of chaperone proteins or bi-specific antibodies to transfer therapeutic antibodies to the brain, the

temporary opening of the BBB by chemical means, and the direct injection of antibodies into the CNS by means of time-released pumps are some of the possibilities to increase antibody delivery across the BBB.

Second, to prevent clogging of the clearance pathway during long-term treatment, a better understanding of the clearance of Aβ/anti-Aβ immune complexes is required. Active vaccination requires attention to the effects of immunotherapy, including immuno-degeneration in the elderly, the potential for autoimmune effects in self-protein vaccination and the use of very strong, pro-inflammatory adjuvants.

Conclusions

After the failure of amyloid-beta targeted therapy across many different clinical trials, tau immunotherapy has become the focus in the recent treatment of Alzheimers and other taupathies [9]. Tau offers many versatile targeting options that have been implicated as playing key roles in the disease process [27]. As discussed previously there are currently many active and passive immunotherapy vaccines that are in clinical trials or in development. These immunotherapies target intracellular and extracellular tau with varying affinities which could possibly translate into clinical efficacy. In fact, some vaccines that are in clinical trials and some which are also in development have chosen to target aggregated tau proteins in addition to the monomeric form. This represents an important milestone in tau immunotherapy as these newer antibodies have the ability to prevent 'seeding' and 'prionosis', which have been theorized to be the key mechanism behind the progression of the disease [28]. Currently, most of these therapies are in either phase II or III will complete it within the next two years. Once these promising therapeutics have completed the phase III trial, we can accurately understand the effect these "vaccines'' will have on the clinical syndrome of the disease. And since tau proteins have been identified to be accumulating decades before the symptoms of the disease arise, it enables us to think about screening or even prophylaxis. We might be able to vaccinate the general population against taupathies or even be able to identify early biomarkers that can allow giving this vaccine in the very early stages of the disease. There is also a very significant chance that tau targeting might be an unfruitful avenue to pursue and could yield the same results as amyloid-beta targeting. Given the multifactorial and polygenic nature of tauopathies, we multiple targeting options might have to be combined to possibly halt the progression of the disease [12]. More research into the pathogenesis and pathophysiology of tauopathies can help to refine current targets and to develop novel ones.

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