Central

**Tau Targeting Therapy in Alzheimer’s Disease**

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**Abstract**

Alzheimer’s disease (AD) is the most common form of dementia. Amyloid plaques and neurofibrillary tangles are the characteristic pathology in AD, the amyloid plaques and neurofibrillary tangles causes the synaptic and neuronal loss, causing dementia. There is still neither efficient therapy for AD treatment nor preventive therapy available. Aβ (Amyloid beta) and tau are the main targets for therapy. Since long therapies targeting Aβ was the main focus of trial, but in recent year’s therapy targeting tau is getting importance, due to failure of agents targeting Aβ. In this article the various strategies targeting tau and their therapeutic value is discussed.

**ABSTRACTIONS**


**ALZHEIMER’S DISEASE**

Alzheimer’s disease is the most prevalent disease of all dementia. As the population, ages, the number of affected people is expected to increase dramatically, making it a global problem worldwide [1]. By the time AD is diagnosed, there is extensive neuronal loss and irreversible brain damage, making the currently available treatment only symptomatic, without blocking or progression of the disease. The currently available drugs slightly improve cognition and dimprove the quality of life temporarily. Till now no new drugs have developed and approved for use, though several clinical trials have failed [2]. There are many research and efforts to develop disease modifying therapies for AD targeting at Aβ cascade hypothesis, tau and neurofibrillary tangles [3]. In AD cognitive deficits, it has been shown that tau pathology correlates better than Aβ pathology, with the progression of AD, and failure of drugs targeting Aβ pathology, the focus of drug trials have been switched towards tau [4].

Tau is a stabilizing microtubular protein discovered in 1975 [5]. Tau is normally a highly soluble cytoplasmic protein that interacts with microtubules to stabilize the cytoskeleton and regulate axonal transport. When it is modified by abnormal phosphorylation and dissociation from microtubules, is the key mechanism in causing tau pathology in AD and other related taupathies. Pathological tau species show altered interaction and localization and loss of physiological function, that promotes progressive appearance of tau pathology [6,7]. Phosphorylation of tau by kinases, or by phosphatases, may be suitable targets for therapy in AD. However because of substrate specificity and several regulatory subunits, Phosphatase is not amenable to drug therapy [8].

**KINASES**

Tau is phosphorylated by different kinases like GSK3B, cdk5, ERK and Dyrk I 1A. Some small molecule inhibitors targeting GSK3B like SRN003-556, CHIR-98014 AND SB 216763 are also in experimental stage. Aβ activates GSK3B and hyperphosphorylates tau and subsequently neuronal death [9]. In transgenic mice, lithium or NP12, a pharmacological inhibitor of GSK3B causes a reduction of tau phosphorylation and NFT formation [10]. Basing on this the trial of lithium ion PSP and CBD was discontinued due to its poor tolerability [11]. TidegUSB, an inhibitor of glycogen synthase kinase 3 (GSK3-β) and its use will counteract tau hyperphosphorylation by inhibiting GSK3-β. In preclinical studies, tidegUSB was reported to reduce a range of disease outcomes, including tau phosphorylation, amyloid deposition, neuron loss, and gliosis in mouse entorhinal cortex and hippocampus, and to reverse a spatial memory deficit in transgenic mice. Neuroprotective, anti-inflammatory, and neurogenesis-inducing effects of tidegUSB have been reported in animal models, as well [12-14]. It reported good tolerability except for a transient increase in serum transaminase levels. It also reported trends for a cognitive benefit on the MMSE screen and ADAS-Cog test battery [15]. In a phase 11b trial short term (26 weeks) tidegUSB was acceptably safe but produced no clinical benefit in this trial. However, given the non-linear dose response, especially in mildly affected patients, further dose finding studies in early disease stages and for longer duration are warranted [16] .

CDK5 is a protein directed serine/threonine protein kinase. Physiological activation is controlled by binding the regulatory subunits, p35 or p39, to CDK5, leading to brain development and synaptic activity. P35 or 39 is are cleaved by calpain,
producing p25 or p29. The binding of p25 or p29 to CDK5 leads to hyperactivation, and tau phosphorylate [17]. It is seen in a transgenic AD mouse model, silencing of CDK5 by si –RNA, reduced tau phosphorylation [18].

**FYN**

Tau protein has five tyrosine residues that are phosphorylated by tyrosine kinases. Src family kinase, including Fyn, modulates neurotransmitter function and NMDA trafficking [19]. Fyn preferentially phosphorylated TYR18 among the five tyrosine residues in tau [20]. Fyn deficiency reduced tau NFT formation and hyperphosphorylation in mice [21] indicating that Fyn inhibition is a potential target for tauopathy. A large body of evidence has underlined the critical role of Fyn in balancing Tyr phosphorylation content of neuronal neuronal proteins, including Tau and APP [22]. Consistently, the increased tyrosine phosphorylation of target proteins can be blocked by the addition of TK inhibitors suggesting that Fyn hyperactivity might be pharmacologically targeted to delay degenerative processes in AD [23,24]. It has been suggested that the pharmacologic targeting of Fyn may be therapeutically efficacious in dysfunctional neurons in which Fyn activity is impaired [25].

A low molecular weight 0-GlcNAcETYLATION inhibitor, MK-8717 was found to elevate brain 0-GlcNAc, and reduce pathological tau, and ameliorate brain atrophy in an Rtg4510 mouse model of tauopathy [26]. In a clinical trial in 16 healthy controls, MK-8719 was well tolerated [27]. Similarly in it was seen that ASN120290, another OGA inhibitor was found to decrease phosphorylated tau in transgenic mouse model and in a phase 1 trial of 61 healthy volunteers, it was found to be safe and well tolerated [27].

Phosphatidylinositol 3-kinase (PI3K)- Synaptic vesicle protein 2A (SV2A) is an indispensable vesicular protein specifically expressed in synapses and can be used as a biomarker for synaptic density. Evidence gained in the study points to the phosphatidylinositol 3-kinase signaling pathway as a possible mediator in SV2A regulation influencing the incidence and development of AD. With limited effective diagnostic methods for AD, a dose interplay between SV2A and AD-related proteins demonstrated and may provide novel and innovative diagnostic and therapeutic opportunities [28].

**TAU AGGREGATION INHIBITION**

Taupathies involve the formation of mis folded and oligomerized tau, and formation of NFT. NFT gradually accumulates in nerve cell and eventually causes neuronal death.

Tau aggregation inhibitors, prevent tau pathology. Curcumin has anti-oxidant, anti angiogenic, anti-inflammatory and neuroprotective action [29]. Curcumin inhibits amyloidogenic protein aggregation, including Aβ [30], but also tau [31,32]. The inhibitory action of Curcumin in preventing tau aggregation, involves in reduction of tau oligomer level [31] and the interaction to PHF 6 segments [32].

**RESVERATROL**

Resveratrol is a nonflavonoid polyphenol rich in grape skin and wine [33]. In a transgenic mouse model, it was seen that the level of tau phosphorylation at AT8 sites was reduced [34]. Similarly the drug also improved cognitive deficit in P301Stau transgenic mice [35]. Several pieces of evidence have shown in the last decades that RV presents neuroprotective actions in experimental models of AD and PD. However, clinical trials have failed to demonstrate these actions, probably due to the low bioavailability of RV, among other pharmacokinetics characteristics. Different RVD has been generated, including hydroxylated, aminated, amidated, methoxylated, prenylated and glycosylated derivatives. These derivatives are neuroprotective in some experimental models of AD and/or PD; however, more preclinical studies are needed to understand their mechanisms of action and toxicity before testing them in clinical trials [36].

**PURPURIN**

Purpurin, A natural dye is seen to inhibited tau fibrillization by heparin through interaction with PHF6 segment [37]. Purpurin also reduced hTau accumulation in cell culture overexpressing Htau. Importantly, Purpurin efficiently cross-linked an in vitro human blood-brain barrier model; suggest that Purpurin may be a potential lead molecule for AD therapeutics [37]. Similarly Ginseng had shown to inhibit tau aggregation in vitro [38]. Methylene blue, in transgenic mice decreases phosphorylated tau aggregation and prevents memory impairment [39]. In a phase 2 trial of 24 weeks administration of methylene blue (MB) to 321 pts of moderate AD, showed improvement in AD, compared to placebo [40]. However in a phase 3 trial, LMTM, a MB derivative failed to achieve improvement in AD patients [41]. MB actions are limited to inhibition of tau fibril formation provides a mechanistic explanation for the poor performance of MB in the recent Phase III clinical trial [42].

**IMMUNOTHERAPY**

Promising therapeutic effects have been demonstrated in transgenic mice by immunotherapy either active immunization [43] or by passive Immunotherapy [44]. Similarly in a phase I b trial, it was shown that immunotherapy effectively improves cognitive function [45]. The mechanism by which it works still unknown, but it was shown that intracellular tau oligomers were secreted and subsequently taken up by neighboring cells triggering tau oligomerization in receiving cells [46].

**ACTIVE IMMUNOTHERAPY**

Active immunotherapy, while a number of anti tau antibodies used in passive immunotherapy, and are on clinical trials, only two active tau vaccines AADvaci and AC135 are being tested for clinical trials

- AADvaci1, a synthetic peptide having aminoacid s 294-305of the tau reduced tau pathology and behavioral deficits in transgenic rats [47]. In humans, AADvaci proved to be safe, well tolerated in phase i trial. A phase 2 multi center trials to evaluate the efficacy and its safety in patients with mild AD for 24 months, it was found that, vaccine treatment did not improve the cognitive score, functional outcomes, in an analysis for participants of all ages [48]. The CSF changes of phosphorylated tau levels were not statically significant, so a phase 3 trial is planned (Alzforum. org Therapeutics). AC1-35a liposomal vaccine in a phase I b study
PASSIVE IMMUNOTHERAPY

Passive immunotherapy, currently the passive immunotherapy is targeted to extracellular tau species, and is suitable for removing extracellular tau [49]. In transgenic mice, RG73459 (a humanized antibody that recognizes tau phosphorylated at Ser422), was shown to enter neurons and reduce tau pathology [50]. In a phase I trial to assess safety of this antibody, in healthy young individual (US National Library of Medicine. ClinicalTrials.gov) [51], the results of this trial have not been released and the drug has been discontinued by Roche. It was observed that neurons derived from stem cells of patients with familial AD secreted amino-terminal tau fragments, termed e-tau, BIB092 [52]. When added to the media of cultured neurons, these fragments induced hyperactivity and increased Aβ production, and these effects were blocked by the application of an antibody recognizing residues 9-18 of e-tau. A phase I study showed marked reduction in CSF free-N terminal tau post immunization in healthy participants and in PSP [53]. A phase II trial aiming to study the clinical efficacy of BMS-96168 in 400 patients with PSP [54].

In cell culture, C2N-8E12 prevented pathological tau seeding caused by exogenous tau aggregates [55]. Infusion of this antibody into the brain in a transgenic mouse model of tauopathy reduced the levels of aggregated and hyperphosphorylated tau and improved cognition [56]. Phase I testing of C2N-8E12 in patients with PSP did not show any major adverse effects or safety issues compared with placebo (US National Library of Medicine. ClinicalTrials.gov https://clinicaltrials.gov/show/NCT02880956 [2018]) [57]. A phase II trial is ongoing. Phase I safety assessments of RO 7105705 are being conducted in healthy individuals and in patients with AD (US National Library of Medicine. ClinicalTrials.gov https://clinicaltrials.gov/show/NCT03019536 [2018]) [58].

BIB076, a human monoclonal anti tau antibody recognizes monomeric and fibrillary tau. A phase I trial is on the way to find out the safety of BIB076 in healthy volunteers and AD patients. Eli Lilly initiated two phase I trials to study the safety and pharmacokinetics of the anti-tau antibody LY3303560, one in healthy individuals and patients with AD [59] (US National Library of Medicine. ClinicalTrials.gov https://clinicaltrials.gov/show/NCT02754830 [2018]) and the other in patients with MCI or AD [60] (US National Library of Medicine. ClinicalTrials.gov https://clinicaltrials.gov/show/NCT03019536 [2018]).

LY3303560 is a humanized anti tau monoclonal antibody, its proto type being monodonal anti mouse MCI. In vivo studies had shown that MCI injection reduced tau pathology in transgenic mice [62], and the mechanism of action is thought to involve binding and removal of extracellular PHF tau. To date a phase I trial of LY3303560 has been conducted to evaluate the safety in MCI and mild to moderate Alzheimer’s disease, while phase II trial is ongoing in early symptomatic Alzheimer’s disease. The results are awaited.

Reduction of tau levels, hyper phosphorylated tau detach from microtubules, causing increase in unbound tau, and mislocalization. It undergoes conformational changes, and forms toxic aggregates and fibrils [63]. It has been proposed that decreasing total level of tau by specific antisense oligonucleotide targeting tau might be a therapeutic target for Alzheimer’s disease, as seen in animal studies [64]. However, human therapies are challenging with antisense oligonucleotide due to its uptake, low stability, vulnerable to degradation and poor blood brain barrier crossing [65]. ASOs that has proven to be neuroprotective and reduce neuronal loss in tau transgenic mice [64,65]. BIB080 an ASO is in phase I trial to address the safety, pharmacodynamics of the drug in mild Alzheimer’s disease (NCT03186989).

CONCLUSION

Till now no drug targeting tau in Alzheimer’s disease have been found to be effective. In the search of disease modifying drugs for Alzheimer’s disease, and other tauopathies, multiple avenues need to be further explored. It is seen that many of the compounds under trials, have effects through more than one pathway. It is also seen that despite having in animal models, it failed to be translated in patients. Further research is required on tau directed treatment to circumvent these problems. Clinical trials may be required to find out more regarding tau pathology, other drugs or combination of strategy, so as to have maximum therapeutic values, so also to minimize the adverse effects. Further trial is also needed to develop therapies once the symptoms have progressed, that is from the MCI stage or very early stage of Alzheimer’s disease.

REFERENCES


