Initial failures of anti-tau antibodies in Alzheimer's disease are reminiscent of the amyloid-β story

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Tau is an important protein of the central nervous system formed by 352–441 amino acids and encoded by the MAPT (microtubule-associated protein tau) gene on chromosome 17 which generates 6 isoforms. Tau is located in axons, dendrites, nucleus, cell membrane, and synapses of neurons. The protein is also expressed to a lesser extent in astrocytes and oligodendrocytes, although its role in these cells has been little investigated. The protein is also present in the interstitial fluid and can cross into the cerebrospinal fluid (CSF) and reach the systemic circulation. The main function of tau is promoting the assembly and stabilization of microtubules in neuronal axons. Tau plays also a role in a range of other biological processes including myelination, neurogenesis, motor function, learning, and memory (Kent et al., 2020). The binding of tau to microtubules is regulated by its phosphorylation/depolymerization equilibrium. In physiological conditions, tau is unfolded and phosphorylated, while the pathological form is characterized by an excess of hyperphosphorylation leading to disengagement from the microtubules, and conformational changes that lead to the formation of paired helical and straight filaments of abnormally phosphorylated tau and subsequently to tau aggregates. These aggregates can cause degeneration of neurons and glial cells that ultimately lead to various clinical cognitive, behavioral, and motor manifestations, which are classified into different types of neurodegenerative disorders called ‘tauopathies’. Tauopathies are classified into primary and secondary tauopathies. In primary tauopathies, the abnormal tau accounts for the primary underlying neurodegenerative process. Primary tauopathies include progressive supranuclear palsy (PSP), corticobasal degeneration, corticobasal syndrome tauopathy, Pick's disease, frontotemporal dementia, frontotemporal lobar degeneration, primary progressive aphasia, MAPT mutation, argyrophilic grain disease, and primary age-related tauopathy. In secondary tauopathies, tau neuronal inclusions occur in association with the extracellular deposition of a second aggregated protein. Secondary tauopathies include Alzheimer’s disease (AD) and Down syndrome (in which amyloid-beta accumulates), Lewy body dementia (in which α-synuclein accumulates), and chronic traumatic encephalopathy (in which TAR DNA-binding protein 43) accumulates.

Recently, it has been shown that tau is differentially phosphorylated in various tauopathies. In the brain of AD patients, there is increased phosphorylation at positions Ser202, Thr231, and Ser265, while Pick’s disease brains show increased phospho-Ser202, and argyrophilic grain dementia brains show increased phospho-Ser396. In neurodegenerative tauopathies, pathological tau can propagate between neuroanatomically connected brain regions by multiple mechanisms, spreading tau pathology throughout the brain. However, recent neuropathological studies in the AD brain suggest that local replication, rather than spreading between brain regions, is the main process driving the overall rate of tau accumulation in neocortical regions. There are also contrasting theories as to whether it is soluble or aggregated tau species that correlate with disease progression and cognitive decline in AD patients.

No drugs have yet been approved for the treatment of primary tauopathies. The treatments currently used are mostly off-label medications targeting symptomatic management, with only minimal evidence from controlled trials to support their use. However, recent advances in the clinical, neuropathological, and biochemical characterization of tauopathies have prompted the search for disease-modifying therapies. In the last 15 years, the search for drugs interfering with pathological aggregation, processing, and communication of tau has been particularly intense. More than 30 drugs have reached the clinic including two tau aggregation inhibitors, three microtubule stabilizers, three glycogen synthase kinase-3β inhibitors, one tau acetylation inhibitor, three O-GlcNAcase inhibitors, two anti-tau active vaccines, 11 anti-tau monoclonal antibodies, one tau antisense oligonucleotide, and one progranulin enhancer (Figure 1A). Unfortunately, to date none of these pharmacological approaches have produced clinical benefits in patients. Major efforts have been devoted to the development of passive immunotherapeutic approaches to stimulate brain clearance of tau and phosphorylated tau aggregates, and several anti-tau monoclonal antibodies directed against different tau epitopes (Figure 1B) have also been tested. Studies in animals have suggested that the therapeutic efficacy of tau immunotherapy may depend on the precise tau region that is targeted, with behavioral effects not directly correlating with the reduction in tau pathology burden. Up to now, controlled trials of anti-tau antibodies in both primary (mainly progressive supranuclear palsy) and secondary (mainly AD) tauopathies have failed to show clinical efficacy.

Among 12 anti-tau therapies in development for AD, a Phase 2 trial of semorinemab, a humanized anti-tau antibody against the N-terminal epitope, showed no differences in the rates of cognitive decline of prodromal or mild AD patients compared with placebo (Mullard, 2021). Gosuranemab, another monoclonal antibody targeting the N-terminal region of tau, even worsened cognitive decline in patients with early stages of AD (Shulman et al., 2021). The development of zagotenemab, whose primary epitope is in tau's N-terminal region, was recently discontinued due to its failure to positively affect cognitive decline in a Phase 2 study in early AD. Thus, all monoclonal antibodies targeting the N-terminal region of tau (semorinemab, gosuranemab, tilvanemab, zagotenemab) have failed in major clinical trials in AD or other tauopathies. The reasons for these failures are not clear, but we know that the N-terminal domain of tau provides spacing between the microtubules and this activity may be vital for the physiological function of tau. Thus, attacking this specific epitope of tau with selective antibodies may not produce clinical benefits. The scientific community is now directing its efforts to other regions of the tau protein. Mid-region antibodies are believed to have more chance of interfering with the cell-to-cell propagation of pathogenic, aggregated tau than do N-terminal anti-tau antibodies. More recently it has been proposed that antibodies binding the microtubule-binding region, which spans residues 224–369, may be better at preventing aggregations from spreading (Horie et al., 2021) and several such antibodies have now entered Phase 1 or 2 clinical testing.

Failed clinical trials with anti-tau monoclonal antibodies in AD have provided potentially important information for future investigations. In a failed trial of semorinemab in 457 early AD (TAUREL study), the antibody elicited maximal increases in plasma tau, indirectly indicating a possible transfer of soluble tau from CNS to plasma, but did not slow tangential accumulation in brain as measured with the tau PET tracer guanosine triphosphate 1, relative to placebo. In another failed trial of gosuranemab in 654 subjects with early AD (TANGO study), the drug was shown to engage its target because the CSF level of N-terminal tau fragments fell in the active treatment group but, again, no effect on tau accumulation was detected by tau-PET scans and accelerated cognitive decline was seen to occur (Shulman et al., 2021). Interestingly, another trial of semorinemab in 273 subjects with moderate AD (LAURIEL study) produced a signal of partial efficacy with a 4.2% reduction in the rate of cognitive decline as measured by the Alzheimer’s Disease Assessment Scale, Cognitive Subscale, 11-item Version from baseline to 49 weeks compared to placebo. On the other hand, the...
antibody did not show any improvement relative to placebo on the other co-primary functional endpoint, the Alzheimer’s Disease Cooperative Study-Activities of Daily Living. It also did not improve secondary endpoints including cognition with the Mini-Mental State Examination, or global performance as measured by the Clinical Dementia Rating-Sum of Boxes (CDR-SOB). Unfortunately, these findings did not make clear whether the drug affected tau-PET. Nevertheless, these findings do suggest that anti-tau immunotherapies that reduce soluble tau species in plasma, compared with placebo. Nevertheless, the trial was stopped early due to prespecified futility analysis, suggesting that efficacy was unlikely to be demonstrated. In the 1-year gosuranemab trial involving 486 participants, a positive effect of the monoclonal antibody on PSPRS5 was not shown in this study. Two interim tau levels (between 25 and 11 centiloids) in decreasing by 98% with gosuranemab and increasing by 11% with placebo (Dam et al., 2021).

If these negative results are confirmed with other anti-tau antibodies or antisense oligonucleotides, we have to conclude that lowering soluble tau does not produce clinical benefits in either PSP or AD. This may mean that the tau contribution to neurodegeneration is due to a loss of its function at the microtubules. This would mean that soluble tau is not causing clinical symptoms and represents an epiphenomenon of the true pathophysiological process. However, some investigators have suggested that these clinical failures may be due to much better than in other tauopathies (factorial design for testing combinations of anti-tau and anti-Aβ drugs), better clinical measures (more sensitive composite scales), better tau epitope specificity, and use of preclinical/transgenic (mild-tomoderate) models toward worsening in patients on the higher dose of tilavonemab (4000 mg) compared to the placebo arm. Previous work in transgenic mice expressing human tau showed that only slowly progressive tau pathology, reduced loss of brain volume, and augmented cognitive performance. In the Phase 2 trial, target engagement by tilavonemab was shown through changes in CSF and homogenate in plasma, compared with placebo. Nevertheless, the trial was stopped early due to prespecified futility analysis, suggesting that efficacy was unlikely to be demonstrated. In the 1-year gosuranemab trial involving 486 participants, a positive effect of the monoclonal antibody on PSPRS5 was not shown in this study. Two interim tau levels (between 25 and 11 centiloids) in decreasing by 98% with gosuranemab and increasing by 11% with placebo (Dam et al., 2021).

In conclusion, it is our opinion that we should question the assumption that in AD or other tauopathies Aβ deposits or tau aggregates represent causative biomarkers of disease, and that the elimination of Aβ or tau aggregates marking disease progression. Previous studies have shown that there is a lack of correlation between clinical symptoms or neuronal loss and brain Aβ burden in AD and between clinical symptoms or neuritic plaque burden (Mini-Montuori et al., 2021). The most convincing argument against the thesis that brain pathology findings in AD or other tauopathies explain clinical symptoms arises from clinical trials of putative disease-modifying drugs that significantly reduce aggregate pathology but do not elicit clinical benefit indeed, in some cases even causing worsening symptoms (Panza et al., 2019). While most of the pharmacological evidence for this has come from anti-Aβ approaches in AD over the past two decades, in recent years early evidence has been accumulating that anti-tau antibodies have real effect in tauopathies. Tau accumulation is a terminal event in neurodegenerative disorders, and because the increase of CSF tau in patients with AD occurs closer to the onset of clinical symptoms than the decrease of Aβ, it is reasonable to conclude that a greater extent with dementia than Aβ, with tau aggregates predicting dementia better than Aβ deposits (Desikan et al., 2021). Despite a quite large series of negative Phase 2 and 3 clinical trials with anti-Aβ drugs in AD (Panza et al., 2019), the conviction that the accumulation of supposedly toxic proteins (Aβ and tau) is the only pathogenic factor causing clinical symptoms has continued to drive massive discovery pipelines. It is time to reconsider subjecting patients to the removal of physiological levels of soluble Aβ and tau, to concentrate our efforts on Aβ and tau, to understand why, in AD and tauopathies, Aβ and tau begin to aggregate in the brain to form deposits.

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References

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