Movement Disorders
CLINICAL PRACTICE
REVIEW

Disease-Modifying Treatments for Progressive Supranuclear Palsy

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ABSTRACT: In recent years, research has focused on the development of disease-modifying treatments for PSP, targeting mainly at tau dysfunction. However, the glycogen synthase kinase 3 inhibitor, tideglusib, and the microtubuli stabilizer, davunetide, both failed to show efficacy in recent double-blind, placebo-controlled studies. Despite these results, further agents targeting tau dysfunction, tau post-translational modifications, or aiming at mictorubuli stabilization are currently being investigated. Further approaches under development include agents to reduce tau levels extracellularly by active or passive immunization, antisense oligonucleotides to reduce tau concentrations, and small interfering RNAs to suppress human tau expression. However, the major limitation on the way to find disease-modifying treatments for PSP still remains the lack of biomarkers. Indeed, for all of these potential therapeutic modalities, a well-designed human trial would require validated biomarkers, without which the results of negative efficacy trials will be difficult to interpret. In this regard, PET imaging using tau-specific ligands may be proven useful in the near future. There is great hope that the next decade will bring the first effective therapy for PSP.

Fifty years after the first description of PSP, and although our knowledge on genetics, pathophysiology, and clinical spectrum of PSP has expanded,[1,2] there are still no effective treatments available. For almost four decades, treatment approaches focused on neurotransmitter replacement strategies.[3] Despite the poor methodology of most of these studies, it is widely accepted that symptomatic drugs targeting dopaminergic, cholinergic (physostigmine, donepezil, and rivastigmine), or gamma-aminobutyric acid-ergic (gabapentin) deficits are not effective in PSP.[3–5]

As in most sporadic neurodegenerative conditions, research has focused in recent years on the development of disease-modifying treatments.[6] In PSP, the targets of such treatments have been aimed mainly at tau dysfunction.[7–10] Tau-related neurodegeneration may occur by gain of function when tau aggregates, which may be toxic for cells. Tau hyperphosphorylation may promote aggregation of insoluble tau species and decrease microtubule binding, leading to loss of function. Thus, treatment strategies have targeted inhibition of aggregation and/or phosphorylation, reduction of tau levels, and microtubule stabilization.[11–14]

Glycogen synthase kinase 3 (GSK-3) is a kinase important in tau hyperphosphorylation[12,13,15,16] and its inhibition has been found to reduce tau phosphorylation in vitro and in vivo.[11,12,17,18] A trial with lithium, a GSK-3 inhibitor, however, was not tolerated and the study was terminated. Tideglusib, another GSK-3b inhibitor, failed to show efficacy on clinical endpoints in a recent double-blind, randomized, placebo-controlled, phase II clinical trial in PSP[17]; however, there were treatment-related differences in progressive brain atrophy in a small subgroup of patients who underwent longitudinal volumetric MRI scans as part of the study,[19] suggesting that further studies with kinase inhibitors might be warranted. Methylene blue, which has been purported to act by inhibiting tau aggregation, but could also reduce tau levels through enhanced autophagy or other mechanisms, is currently being investigated in phase III clinical trials for Alzheimer's disease and behavioral variant frontotemporal dementia.[20] Moreover, modulating post-translational modifications of tau, such as acetylation, glycation, and O-linked N-acetylglucosamine modification, may represent further promising approaches.[21,22]

Stabilization of microtubules has been proposed as a strategy to compensate for loss of tau function.[23] However, recently, davunetide, a peptide derived from the growth factor activity-dependent neurotrophic protein, which was reported to promote microtubule stability, failed to show efficacy in a 1-year, double-blind, parallel-group, phase II/III, placebo-controlled study with 313 participants.[24] Further microtubule stabilizers,

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such as taxol derivatives (TPI-287), epothilones (mainly epothilone D), and others, are currently being investigated as therapies for tau-related neurodegeneration (for review, see a previous work[20]).

Transcellular spread of altered conformations of tau with prion-like properties has recently emerged as a possible mechanism in sporadic neurodegenerative disorders and offers new therapeutic possibilities for PSP.[25–28] Different strains of pathogenic tau conformations may help to explain the selective vulnerability of different brain networks in the spectrum of tau-related neurodegenerative disease.[29] Therapeutic agents are being developed to reduce tau levels in the extracellular space either by active or passive immunization,[30–32] and evidence from animal models is promising.[33,34] Antisense oligonucleotides (ASOs) have also demonstrated great promise in reducing tau concentrations and their pathogenic consequences in animal models,[35]and intrathecally delivered ASOs have been shown to be well tolerated in amyotrophic lateral sclerosis, suggesting this approach may be feasible for PSP as well.[36,37] Last, experimental data suggest that small interfering RNAs suppressing human tau expression might be another therapeutic option in the future.[38]

Apart from targeting tau, mitochondrial dysfunction has been a therapeutic target of PSP, based on in vitro and in vivo evidence of complex I dysfunction.[39–44] A small, double-blind, placebo-controlled, randomized trial administering coenzyme Q10 for 6 weeks found improved clinical scales as well as occipital energy levels in magnetic resonance spectroscopy[45]; however, a larger, placebo-controlled trial of coenzyme Q10 in 62 PSP patients for 12 months, using clinical scales as primary outcomes, was reported to be negative (poster communication).[46]

Despite the current lack of an effective treatment, new knowledge on the pathophysiology of PSP has contributed to the design of a relative wealth of potential new therapies, the translation of which into humans is well underway. However, despite the fact that PSP is an ideal disease to study tau-related, disease-modifying treatments,[20] current limitations for conducting clinical trials include the late diagnosis and lack of validated biomarkers. In particular, for all of these potential therapeutic modalities, a well-designed human trial would require validated biomarkers of target engagement to demonstrate that therapies exert their predicted biological effect in humans. Without such biomarkers of target engagement, the results of negative efficacy trials will be difficult to interpret. PET imaging using tau-specific ligands and cerebrospinal fluid biomarkers[47] may be proven useful in the near future. There is great hope that the next decade will bring the first effective therapy for PSP.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

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