

Advances in neuroimmunology in the treatment of progressive supranuclear palsy: a systematic review of monoclonal antibodies

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Vitório Serafim¹, Gabriela Bezerra Sorato¹, Henrique Werner Balbinot¹, Ítalo Santos Vieira¹, Guilherme da Rosa Raya¹, Ana Júlia Rodrigues Ribeiro, Ana Carolina Gomes Petry¹, Jessica Vargas Lopes¹, Tábata Smagala¹, Liana Lisboa Fernandez².
(1) Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, Brazil.
(2) Department of Basic Health Sciences, Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, Brazil.

Target Engagement Without Clinical Efficacy: The Translational Gap of N-Terminal Tau Monoclonal Antibodies in PSP																				
INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES																
PSP is a rare, fatal neurodegenerative tauopathy with no approved disease-modifying therapies. The spread of tau pathology, potentially mediated by extracellular N-terminal (N-t) tau, is a key therapeutic target. Monoclonal antibodies emerge as a treatment option for this disease. Figure 1. Proposed mechanism of tau propagation in PSP and therapeutic target of monoclonal antibodies. Extracellular N-terminal tau is hypothesized to mediate the spread of pathology between neurons. Gosuranemab and tilavonemab were developed to neutralize this fraction of tau and interrupt disease progression.	A systematic review was conducted using the PubMed, Embase, and Cochrane databases, with the terms “progressive supranuclear palsy,” “monoclonal antibody,” and their variations, connected by the Boolean operator AND. The inclusion criteria were cohort studies or randomized trials, while the exclusion criteria involved studies with patients presenting associated psychiatric or neurological comorbidities, interventions other than monoclonal antibody therapy, and abstracts without full-text articles. The Rayyan platform was used for blinded screening by two reviewers. Among the 713 articles identified, after removing duplicates, only 3 met the inclusion and exclusion criteria.	All studies reported acceptable safety profiles, similar to placebo. Boxer et al. established robust target engagement for gosuranemab, reducing unbound CSF N-t tau by 91–97% at day 85. This potent biochemical effect was confirmed by Dam et al., which showed a 98.11% reduction in unbound CSF N-t tau at week 52 (P<0.0001). Despite this, Dam et al. failed its primary efficacy endpoint: the adjusted mean change in the PSPRS score at week 52 was 10.4 (gosuranemab) versus 10.6 (placebo) (Difference -0.2, P=0.8483). Secondary endpoints were also negative. Similarly, Höglinger et al. assessing tilavonemab confirmed target engagement with significant reductions in CSF free tau (P<0.0001). However, this trial also failed its primary PSPRS endpoint (4000mg vs placebo: Diff 1.0, P=0.46) and was terminated early for futility.	N-t tau monoclonal antibodies gosuranemab and tilavonemab successfully and potently engage their target in the CSF of PSP patients and are well tolerated. However, Dam et al. and Höglinger et al. conclusively demonstrate that this specific mechanism, neutralizing extracellular N-terminal tau, does not translate into clinical efficacy or slow disease progression in symptomatic PSP. Figure 2. Effect of monoclonal antibodies on free N-terminal tau in cerebrospinal fluid (CSF). <table><tr><th>Study</th><th>Antibody</th><th>Time Point</th><th>Reduction (%)</th></tr><tr><td>Boxer et al., 2019</td><td>Gosuranemab</td><td>Day 85</td><td>91 – 97%</td></tr><tr><td>Dam et al., 2021</td><td>Gosuranemab</td><td>Week 52</td><td>98.11%</td></tr><tr><td>Höglinger et al., 2021</td><td>Tilavonemab</td><td>Week 52</td><td>Significant reduction (P < 0.0001)</td></tr></table> All studies demonstrated robust target engagement, with reductions greater than 90% in free N-terminal tau levels in the central nervous system.	Study	Antibody	Time Point	Reduction (%)	Boxer et al., 2019	Gosuranemab	Day 85	91 – 97%	Dam et al., 2021	Gosuranemab	Week 52	98.11%	Höglinger et al., 2021	Tilavonemab	Week 52	Significant reduction (P < 0.0001)	Dam T, Boxer AL, Golbe LI, et al. Safety and efficacy of gosuranemab in progressive supranuclear palsy: a phase 2, randomised, double-blind, placebo-controlled trial. The Lancet Neurology. 2021;20(2):95-107 Hoglinger GU, Respondek G, Stamelou M, et al. Clinical trials in progressive supranuclear palsy: we are ready. The Lancet Neurology. 2019;18(11):982-984. Congdon EE, Sigurdsson EM. Tau-targeting therapies for Alzheimer's disease and other tauopathies. Nature Medicine. 2021;27(10):1665-1673.
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CONTACT																				
Vitório Serafim. 7th semester Medical Student at the Federal University of Health Sciences of Porto Alegre (UFCSPA) +55 (48) 99915-4220 vitorio.serafim@ufcspa.edu.br  																				

CONTACT

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