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Pilot Trial of Perampanel on Peritumoral Hyperexcitability in Newly Diagnosed High-grade Glioma

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Abstract

Purpose: Glutamatergic neuron-glioma synaptogenesis and peritumoral hyperexcitability promote glioma growth in a positive feedback loop. The objective of this study was to evaluate the feasibility and estimated effect sizes of the targeted AMPA receptor antagonist perampanel on peritumoral hyperexcitability.

Experimental design: An open-label trial was performed comparing perampanel with standard of care (SOC) in patients undergoing resection of newly diagnosed radiologic high-grade glioma. Perampanel was administered as a preoperative loading dose followed by maintenance therapy until progressive disease or up to 12 months. SOC treatment involved levetiracetam for 7 days or as clinically indicated. The primary outcome of hyperexcitability was defined by intraoperative electrocorticography high-frequency oscillation (HFO) rates. Seizure freedom and overall survival were estimated by the Kaplan-Meier method. Tissue concentrations of perampanel, levetiracetam, and correlative biomarkers were measured by mass spectrometry.

Results: HFO rates were similar between patients treated with perampanel and levetiracetam. The trial was terminated early after a planned interim analysis, and outcomes assessed in 11 patients (seven perampanel treated; four treated with SOC). Over a median 281 days of postenrollment follow-up, 27% of patients had seizures, including 14% maintained on perampanel and 50% treated with SOC. Overall survival in perampanel-treated patients was similar to that in a glioblastoma reference cohort. Glutamate concentrations in surface biopsies were positively correlated with HFO rates in adjacent electrode contacts and were not significantly associated with treatment assignment or drug concentrations.

Conclusions: Glioma peritumoral glutamate concentrations correlated with high-gamma oscillation rates. Targeting glutamatergic activity with perampanel achieved similar electrocorticographic hyperexcitability levels as in levetiracetam-treated patients.

PubMed Disclaimer

Update of

Pilot trial of perampanel on peritumoral hyperexcitability and clinical outcomes in newly diagnosed high-grade glioma.

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