Oral Administration of EHP-101 Promotes Remyelination in the Cuprizone/Rapamycin Mouse Model of Multiple Sclerosis

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BACKGROUND

EHP-101 is an oral lipidic formulation of VCE-004.8, a novel non-psychoactive aminooquinone derivative of synthetic cannabinoid that recently completed a Phase I clinical study (see ACTRIMS Poster P061). VCE-004.8 is a dual agonist of the peroxisome proliferator-activated receptor gamma and cannabinoid type 2 receptors with potent anti-inflammatory and neuroprotective activity. VCE-004.8 has also demonstrated activation of the hypoxia inducible factor pathway in human microvascular endothelial cells, oligodendrocytes, and microglia. In vivo, EHP-101 has been shown to prevent demyelination in different murine models of multiple sclerosis (MS) and was recently shown to induce remyelination in white and gray matter in a mouse cuprizone model with moderate demyelination, fast spontaneous remyelination, and only a 2-week treatment window.

OBJECTIVES

Evaluate the potential of oral administration of EHP-101 to promote remyelination in gray and white matter in the cuprizone/rapamycin (C/R) mouse model of extensive demyelination with slower spontaneous remyelination and a 6-week treatment window.

METHODS

Male C57BL/6J mice (n = 5 [age-matched controls] or 12/group) were treated for 12 weeks (wk) with C/R to cause demyelination of white and gray matter regions of the brain. The mice were then orally administered EHP-101 once daily at 0, 5, 10, and 20 mg/kg for 6 weeks. Thereafter, the brains were harvested and processed for immunohistochemical staining and quantification of myelinated axons in gray matter (hippocampus, cerebral cortex) by proteolipid protein (PLP) staining and white matter (corpus callosum) by paraffinollediamine (PPD) staining.

RESULTS (WHITE MATTER)

EHP-101 induced a significant, dose-related increase in the density of PPD staining in the corpus callosum.

RESULTS (GRAY MATTER)

There was no significant change in the area of PLP staining in the hippocampus and cortex after EHP-101 treatment.

CONCLUSIONS

- Near complete axonal demyelination occurred in gray and white matter after 12 weeks of C/R administration compared to age-matched controls.
- Oral administration of EHP-101 induced significant, dose-dependent remyelination of demyelinated axons in white matter corpus callosum.
- No significant remyelination was found in gray matter hippocampus or cerebral cortex after EHP-101 treatment versus vehicle-treated controls.
- Imaging studies in MS patients have demonstrated convincing correlations between white matter lesions and gray matter atrophy, suggesting that neurodegeneration can be a consequence of demyelination via retrograde degeneration.
- Spontaneous remyelination occurs faster and is more extensive in gray matter lesions than white matter lesions, which may partly explain why there is no effects of EHP-101 on remyelination in gray matter as PLP staining in the vehicle-treated group is almost back to age-matched levels after 6 weeks of treatment.
- These data further support the advancement of EHP-101 into Phase 2 clinical studies as a therapy for treating MS patients.

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