suggest the ME as target for enhancement of endogenous oligodendrogenesis/remyelination.

The authors have nothing to disclose.

P825

Laquinimod treatment enhances myelination and prevents neurodegeneration in the chronic EAE mouse model of MS

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Objective: The aim of this study is to assess the dose dependent effects of preventative laquinimod treatment on inflammation, demyelination and neurodegeneration in the chronic experimental autoimmune encephalomyelitis (EAE) mouse model of multiple sclerosis (MS).

Background: Laquinimod has shown to significantly reduce gadolinium-enhancing lesions in patients with MS. Clinical data so far suggest that laquinimod is safe, well-tolerated and efficacious in reducing MRI measures of disease activity, clinical relapses and progression of long-term disability. Laquinimod treatment has shown a significant beneficial effect in rodents with EAE.

Design/Methods: 8-week-old female Thy1-YFP and PLP_EGFP C57BL/6 mice were treated either with 5, 10, or 25 mg/kg/day of laquinimod or vehicle. Treatment groups received oral gavages of laquinimod dissolved in water at the given concentration six days prior to first immunization of MOG and continued 6 days a week throughout disease. Mean clinical disease scores were monitored throughout. Immune analysis of splenocytes and immunohistochemistry analysis of spinal cord and brain was performed at day 26 and day 41.

Results: Mean clinical disease scores of laquinimod treated mice as compared with vehicle (water)-treated mice, were significantly reduced throughout disease, $P < 0.0001$. No dose dependence effect was observed and 5mg to 25mg laquinimod showed equal effects. Laquinimod treated 26 day EAE animals showed significantly reduced Th1 cytokines: IFN-gama, TNF-alpha, and IL-17; decreased Th2 cytokine IL5; and significantly reduced MMP9. Immunohistochemistry analysis of laquinimod groups showed a significant decrease of microglia, T cells and activated astrocyte numbers. A significant increase in oligodendrocyte numbers, myelin density, and axon numbers was observed in the dorsal column and corpus callosum of laquinimod–treated EAE spinal cord and brain.

Conclusions: Our results show that doses as low as 5mg/kg/day laquinimod have significant beneficial effects in the EAE model, where it enhances oligodendrocyte numbers and myelin density and prevents secondary axonal damage. These results further support laquinimod potential role in the treatment of MS.

Seema Tiwari-Woodruff, Rhusheet Patel, Spencer Moore, Manda Sasidhar have nothing to disclose.

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Nrf2 activators: a novel strategy to promote oligodendrocyte survival in multiple sclerosis?

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Objectives: To investigate the potential of different Nrf2 activators to boost antioxidant enzyme expression in oligodendrocytes and protect them from reactive oxygen species (ROS)-mediated cell death.

Background: Oligodendrocyte damage and loss are key features of Multiple Sclerosis (MS) pathology and oligodendrocytes are particularly vulnerable to ROS-induced oxidative damage and cell death. Hence, a potential therapeutic strategy to protect these cells from ROS-mediated damage is urgently needed. To date, several compounds, including fumurate derivative BG-12, tert-Butylhydroquinone (tBHQ), sulforaphane (SFN) and protandim have potential anti-inflammatory and neuroprotective properties. These compounds are thought to exert their protective function via activation of the nuclear-factor-E2-related factor-2 (Nrf2) transcriptional pathway, which is involved in the production of antioxidant enzymes necessary for oxidative stress defense. We postulate that distinct Nrf2 activators boost antioxidant enzyme production in oligodendrocytes and limit ROS-mediated oligodendrocyte cell death.

Methods: Primary rat oligodendrocytes and rat and human oligodendrocyte cell lines were treated with different concentrations of BG-12, tBHQ, SFN and protandim. Next, we analyzed the expression of Nrf2-mediated antioxidant enzymes by PCR and Western blot techniques. To study the beneficial effects of the different Nrf2 activators, we first incubated the oligodendrocytes with Nrf2 activators and subsequently exposed them to various concentrations of hydrogen peroxide and measured oligodendrocyte cell survival.

Results:

1. BG-12, tBHQ, SFN and protandim are well-tolerated and strongly induce Nrf2-driven antioxidant enzyme production in oligodendrocytes, with protandim showing the most potent induction.
2. Nrf2 activators are able to protect oligodendrocytes against ROS-induced cytotoxicity.

Conclusions: Our findings indicate that several Nrf2 activators are able to significantly increase antioxidant enzyme production in oligodendrocytes. Interestingly, protandim, a dietary supplement consisting of herbal ingredients, was the most potent inducer and therefore may be the most suited as a therapeutic strategy. Importantly, Nrf2-mediated antioxidant enzyme expression in oligodendrocytes resulted in enhanced oligodendrocyte survival during an oxidative attack.

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Identification of microRNAs that control oligodendrocyte differentiation and maturation in multiple sclerosis brains

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Multiple sclerosis (MS) is an inflammatory-mediated demyelinating disease of the human central nervous system. Generation of new myelin forming cells and repair of myelin are prominent features of some white matter lesions, especially early in the clinical disease course. Remyelination requires the generation of new oligodendrocytes from a well-characterized progenitor cells. These cells, present at reduced levels in chronically demyelinated white