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The monoselective sphingosine-1-phosphate receptor-1 modulator ponesimod enhances remyelination in the cuprizone model of demyelination

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Background: Sphingosine-1-phosphate (S1P1) receptor modulators are used clinically to treat relapsing forms of multiple sclerosis (MS). Selective functional antagonism of the S1PR1 subtype by ponesimod prevents lymphocyte egression from lymph nodes, hence hampering neuroinflammation in MS. Recent findings suggest a potential additional role for ponesimod in the Central Nervous System (CNS) in the differentiation of oligodendrocyte precursor cells (OPC) into mature myelinating oligodendrocytes, and therefore potentially having some effects on remyelination.
Objective: As the Giα-coupled S1P1 receptor is the most prominently expressed S1PR in OPCs, and the S1P1-monoselective receptor modulator ponesimod promotes OPC differentiation, we hypothesized that functional antagonism by ponesimod can induce remyelination*in vivo*.
Methods: Nine-week-old male C57BL/6J mice were fed a 0.3% cuprizone diet for 6 weeks to induce demyelination. Three days before the stop of the cuprizone diet, mice were treated with a daily gavage of ponesimod (1mg/kg, 3mg/kg, or 10mg/kg) or vehicle (0.1% DMSO) for one week during the remyelination phase. The Y maze spontaneous alternations test was applied to test recovery from demyelination-induced working memory deficits at the end of the treatment period. In parallel, de- and remyelination of the optic nerve axon was evaluated by measuring the latency time of visual evoked potentials both during the de- and remyelination phase. Post-mortem remyelination was quantified in an immunohistogical staining for myelin basic protein (MBP) in the corpus callosum, cortex and hippocampus and by determining g-ratios in transmission electron microscopy (TEM) pictures of the corpus callosum.
Results: Ponesimod (1mg/kg, 10mg/kg) decreased the latency time compared to vehicle conditions, which is indicative of functional remyelination. MBP IHC analysis of the corpus callosum (ponesimod 1mg/kg), hippocampus (ponesimod 1mg/kg, 10mg/kg) and cortex (ponesimod 3mg/kg) revealed an increased MBP-positive area. TEM analyses revealed decreased G-ratios in the groups treated with ponesimod 10mg/kg. In addition, the Y maze spontaneous alternations test revealed restored working memory after treatment with ponesimod (1mg/kg, 3mg/kg).
Conclusion: Ponesimod S1P1-monoselective receptor modulator increased remyelination in the cuprizone model of demyelination.

Disclosure
MS, EW ad TV report no competing interest. MAT is an employee of Janssen and may own stock or stock options in Johnson & Johnson.

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Oral administration of a novel small molecule that blocks BMP-signaling ameliorates EAE through oligodendrogenesis and remyelination

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Introduction: Oligodendrocyte precursor cells are present in demyelinated MS lesions. However, their differentiation into functional oligodendrocytes is insufficient, and most lesions evolve into nonfunctional astroglial scars. Parenteral anti-bone morphogenetic protein (BMP) therapy was reported to ameliorate EAE through oligodendrogenesis and remyelination.
Objective: To evaluate the effect of oral administration of a novel anti-BMP small molecule (SM) at different doses in experimental allergic encephalomyelitis (EAE) murine model.
Aims: To measure the effect of SM vs. vehicle on EAE clinical signs, BMP signaling, oligodendrocytes regeneration, and the SM pharmacokinetics
Methods: Different doses of a novel anti-BMP- SM, given daily by oral gavage from day 9 (signs onset) until day 38 to EAE induced SJL mice by $PLP_{139-151}$vs. vehicle (PEG-400), n=12 per group. We analyzed the clinical signs (score 0-5), histopathology by confocal microscopy, and SM pharmacokinetics.
Results: Oral administration at a daily dose of 750 μg or 1500 μg of SM to EAE- induced mice ameliorated the disease scores between days 14-30 ($p<0.05$ for each day) and the cumulative scores (mean±S.E.M) of 44.7±2.9 (p=0.032 and 50.3±6.6 p=0.05, respectively vs. 72.3±12.7 in vehicle). The expression of the BMP-signaling transducer phospho-SMAD1/5/8 was reduced after treatment with oral SM in astrocytes (15.0±4.9 cells/mm^2vs. 43.8±4.2 cells/mm^2 in-vehicle, p=0.001) and in oligodendrocytes (14.5±6.9 cells/mm^2vs. 41.4±4.5 cells/mm^2, respectively, p=0.009). Oral SM