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IRX4204 enhances gait recovery in mice subjected to experimental autoimmune encephalomyelitis

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Introduction: Current immune-based therapies for multiple sclerosis (MS) reduce relapses but have limited value in slowing disease progression. Remyelination is considered essential for functional recovery in MS. Activation of the retinoid X receptor (RXR) enhances remyelination by increasing the production of myelin-producing oligodendrocytes. 3-Methyl-5-[(1S,2S)-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl]-2(E),4(E)-pentadienoic acid (IRX4204) is an investigational drug that preferentially activates the RXR.

Objective: The purpose of this study was to determine if IRX4204 administration improves motor recovery and remyelination in a mouse model of MS termed experimental autoimmune encephalomyelitis (EAE).

Methods: Female C57Bl/6 mice (20-25 g) were subjected to EAE by immunization with a peptide corresponding to amino acids 35-55 of myelin oligodendrocyte glycoprotein. A solution containing 3 mg/mL of this peptide in phosphate buffered saline (PBS; pH 7.4) was emulsified (1:1 ratio) in Complete Freund's Adjuvant (CFA). Each mouse received two 100 μL injections of the emulsified mixture subcutaneously. Additionally, each mouse received a 200 μL injection of pertussis toxin dissolved in PBS (1.5 ng/μL) on the day of immunization and again on day post-immunization 2. Mice were then treated orally with either vehicle (NEOBEE; 8 ml/kg/day; n = 10) or IRX4204 (12 mg/kg/day; n = 10) beginning at peak disease (day post-immunization 16). Disease severity was assessed using a clinical scoring scale and white matter loss was assessed following the staining of spinal cord sections with eriochrome cyanine and neutral red. Motor function was assessed weekly using kinematic gait analysis to measure hindleg movements in the sagittal plane while mice walked on a treadmill. Spinal cord concentrations of IRX4204 following daily doses were measured using liquid chromatography in tandem with mass spectrometry.

Results: Relative to vehicle, IRX4204 reduced clinical scores and reversed gait deficits in EAE mice. Gait improvements in IRX4204-treated EAE mice were characterized by increased toe heights and the recovery of knee joint movements. These gait improvements were associated with reduced white matter loss in the spinal cord suggestive of enhanced remyelination. Furthermore, spinal cord concentrations of IRX4204 reached levels known to stimulate the differentiation of oligodendrocyte progenitor cells into myelin-making oligodendrocytes.

Conclusion: These results support and extend findings from other laboratories which have reported that RXR activation enhances remyelination and reduces motor deficits in mice subjected to EAE. Our findings suggest that IRX4204 may reverse motor deficits in MS by stimulating remyelination.