IRX4204 enhances gait recovery in mice subjected to experimental autoimmune encephalomyelitis.

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Introduction

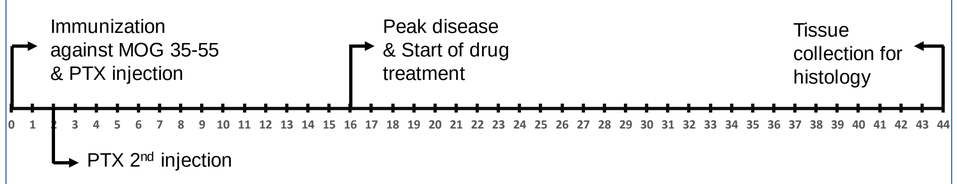
Current immune-based therapies for multiple sclerosis (MS) reduce relapses but have limited value in slowing disease progression. Remyelination is considered essential for functional recovery in MS.[1]

Activation of the retinoid X receptor (RXR) enhances remyelination by promoting the differentiation of oligodendrocyte progenitor cells into myelin-producing oligodendrocytes.[2] IRX4204 is an investigational drug that preferentially activates the RXR and is orally bioavailable.[3]

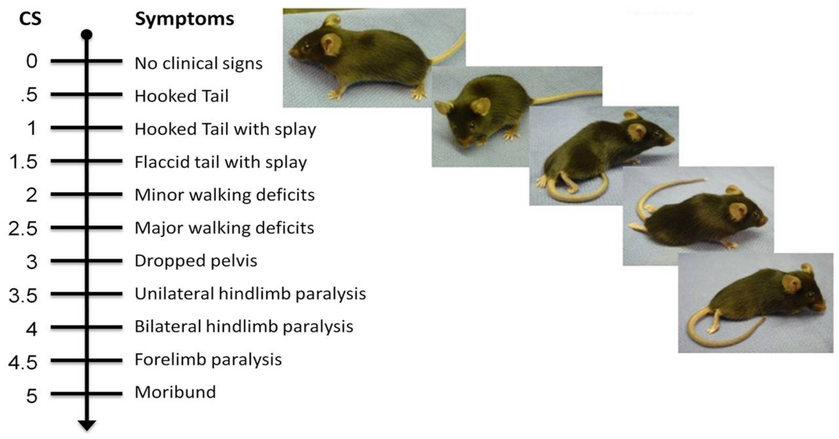
To determine if the oral administration of RX4204 improves motor recovery and remyelination, we tested this drug in a mouse model of MS termed experimental autoimmune encephalomyelitis (EAE). We compared clinical scores, gait, and levels of white matter loss in EAE mice following treatment with either vehicle or IRX4204 beginning at peak disease (day post immunization 16; DPI16).

Methods and Materials

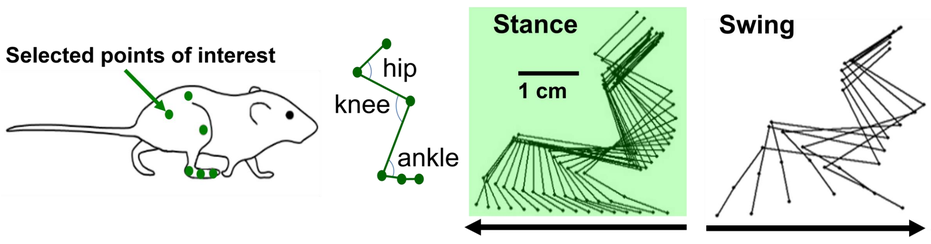
EAE was induced by immunizing mice with a fragment of myelin oligodendrocyte glycoprotein 35-55 (MOG_{35-55}). MOG_{35-55} was emulsified in Complete Freund's Adjuvant and injected subcutaneously at DPI 0. An intraperitoneal injection of pertussis toxin (PTX) was administered concomitantly at DPI 0, and again at DPI 2.



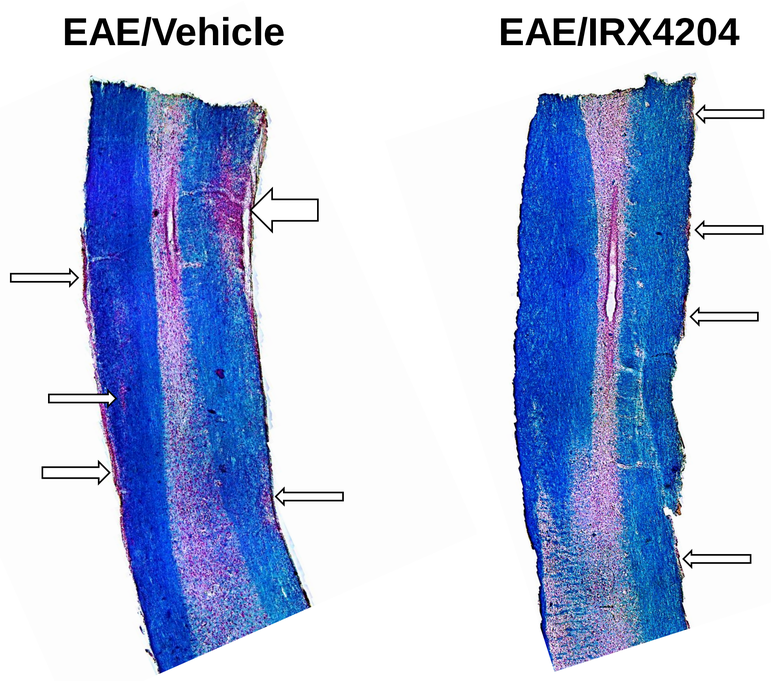
Disease severity was rated daily using an 11-point clinical scoring system as shown below. Areas under the clinical score curves after vehicle or IRX4204 administration were calculated and analyzed using a Mann-Whitney U test.



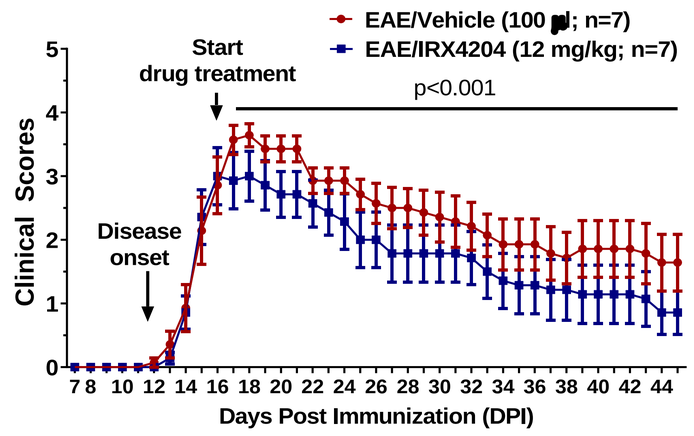
Gait in the sagittal plane was measured by tracking the iliac crest, hip, knee, ankle, metatarsophalangeal joint, and toe of a mouse while walking on a treadmill. Gait parameters were compared between groups at weekly timepoints. A two-way repeated measures ANOVA was used to compare differences between the gait data for vehicle- and IRX4204-treated EAE mice from DPI 23-44.



Representative spinal cord sections from EAE mice treated with vehicle (EAE/Vehicle) or IRX4204 (EAE/IRX4204) and stained with eriochrome cyanine and neutral red to detect white matter. Arrows show regions of white matter loss that were quantified using computer-assisted image analysis and compared for statistical differences using a Mann-Whitney U test.

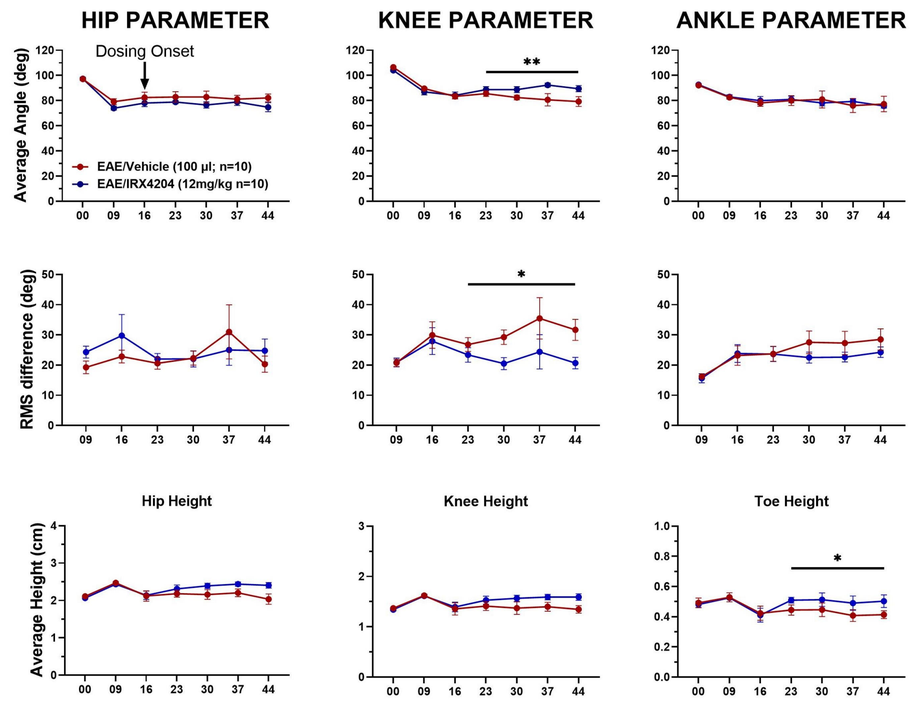


IRX4204 Reduces EAE Disease Severity



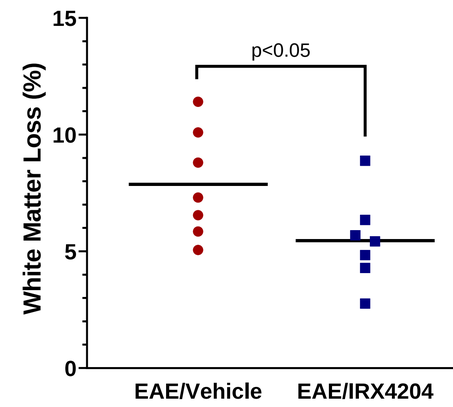
Clinical scores for EAE mice treated orally with vehicle or IRX4204 once daily beginning at DPI 16 and until DPI 44 (mean ± SEM). The clinical scores were lower for EAE/IRX4204 than EAE/Vehicle mice.

IRX4204 Reduces Gait Deficits in EAE Mice



Hip, knee, and ankle angles, range of motion (ROM) and root-mean square (RMS) differences were measured using kinematic gait analysis at DPI 0, 9, 16, 23, 30, 37 and 44 for EAE/Vehicle and EAE/IRX4204 mice (mean ± SEM). Deficits in knee angle, knee RMS differences, and toe height were reduced in EAE/IRX4204 relative to EAE/Vehicle mice.

IRX4204 Reduced Spinal Cord White Matter Loss in EAE Mice



White matter loss in the spinal cord was reduced in EAE/IRX4204 (n=7) relative to EAE/Vehicle (n=7) mice at DPI 44. A Mann-Whitney U test was used to identify statistical differences between the two groups.

Conclusions

Using kinematic gait analysis, our results support and extend findings from other laboratories which have reported that RXR activation reduces motor deficits in mice subjected to EAE.

Relative to vehicle, IRX4204 reduced clinical scores and reversed gait deficits in EAE mice when administered at peak disease. 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.

Our findings suggest that IRX4204 may also reverse motor deficits in MS by stimulating remyelination and thus support the testing of this RXR agonist for clinical efficacy in MS.

References

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