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Antibody-mediated oligodendrocyte remyelination protects axons and restores axonal transport in progressive demyelinating disease

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Background: The precise mechanisms by which axonal injury occurs in multiple sclerosis are unclear; one hypothesis is absence or failure of remyelination, suggesting that promoting remyelination may protect axons from death.
Objective: The objective of the present work is to investigate whether promoting remyelination protects axons and restores transport function.
Methods: Remyelination was induced in Theiler's virus-infected SJL/J mice using an oligodendrocyte/myelin-specific recombinant human monoclonal IgM, rHIgM22. As an indirect measure of spinal cord integrity, brainstem magnetic resonance spectroscopy was performed across treatment groups. At the completion of the experiment, spinal cord morphology (inflammation, demyelination, remyelination and mid-thoracic axon density) was assessed in detail. Retrograde labeling studies were performed on the spinal cord to provide direct evidence that remyelination protected axons.
Results: Brainstem *N*-acetyl aspartate concentrations were increased at 5 weeks post-treatment with rHIgM22, which remained stable out to 10 weeks. Spinal cord morphology studies revealed enhanced remyelination in the rHIgM22-treated group compared to isotype control antibody- or saline-treated groups. Importantly, rHIgM22-mediated remyelination appeared to protect small- and medium-caliber mid-thoracic spinal cord axons from damage despite similar demyelination and inflammation across experimental groups. The most direct confirmation of remyelination-mediated protection of descending neurons was an improvement in retrograde labeling. Treatment with rHIgM22 significantly increased the number of retrograde labeled neurons in the brainstem, indicating that preserved axons are functionally competent.
Conclusion: Our work provides direct evidence that remyelination preserves spinal cord axons, and protects molecular axon trafficking in a chronic murine demyelination model of human multiple sclerosis.

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Walking, quality of life, and safety with prolonged-release fampridine treatment in clinical practice: Interim results of the liberate study

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Background: Impaired walking is common in multiple sclerosis (MS) and negatively impacts patients' lives.
Objective: To collect long-term, real-life data in MS patients treated with prolonged-release (PR) fampridine (dalfampridine extended-release in the United States) in clinical practice.
Methods: LIBERATE is an observational, ongoing study enrolling patients initiating treatment with PR-fampridine 10 mg twice daily in routine clinical practice. Endpoints include patient-perceived impact of MS measured by the Multiple Sclerosis Impact Scale-29 physical subscale (MSIS-29 PHYS) and physician-assessed Clinical Global Impression of Improvement (CGI-I) of walking ability. Safety was also assessed. Patient and/or institutional review board approval was obtained, as necessary. Interim results from France and Germany are reported.
Results: As of July 2014, 1803 patients enrolled in Germany and France of whom 1155 were dosed and completed 6-month follow up (n = 820 remained on-treatment; n = 335 had discontinued treatment but remained on study as patients "off-treatment"). A greater (mean [SD]) improvement in the MSIS-29 PHYS score from baseline to month 6 was observed among patients on-treatment (−8.57 [16.92]; n = 633) versus patients off-treatment (−2.59 [16.85]; n = 238). CGI-I scores improved in 70.1%, remained stable in 22.5%, and worsened in 7.4% of patients on-treatment (n = 582) at Month 6, versus 12.0%, 66.1% and 21.9% of patients off-treatment (n = 192), respectively. The most common adverse events were insomnia (n = 94 [5.2%]), vertigo (n = 64 [3.5%]) and headache (n = 62 [3.4%]).
Conclusions: PR-fampridine was well tolerated and was associated with improved MSIS-29 PHYS scores and walking ability from baseline over 6 months in clinical practice in Germany and France.

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