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Effect of Siponimod on Brain and Spinal Cord Imaging Markers of Neurodegeneration in a Model of Demyelination Caused by Theiler's Murine Encephalomyelitis

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Abstract

Neuroinflammatory demyelinating diseases, such as Multiple Sclerosis (MS), can lead to significant neurodegeneration, causing debilitating neurological symptoms. Siponimod, a selective sphingosine-1-phosphate receptor modulator, has shown promise in the treatment of MS by modulating immune cell trafficking and reducing neuroinflammation. In this study, we investigated the effect of siponimod on brain and spinal cord imaging markers of neurodegeneration using a murine model of demyelination caused by Theiler's Murine Encephalomyelitis Virus (TMEV). Through comprehensive neuroimaging analysis, we evaluated the impact of siponimod on demyelination-associated neurodegeneration, providing insights into its potential as a therapeutic intervention in demyelinating diseases.

Keywords: Siponimod • Spine • Neuroinflammatory

Introduction

Demyelination is a key hallmark of neuroinflammatory disorders like multiple sclerosis, where immune-mediated damage to the myelin sheath leads to axonal loss and subsequent neurodegeneration. Siponimod, a derivative of fingolimod, has demonstrated efficacy in reducing relapse rates and disease progression in patients with relapsing forms of multiple sclerosis. The mechanism of action involves modulation of immune cell trafficking, preventing immune cell infiltration into the Central Nervous System (CNS), and thus attenuating inflammation. However, the impact of siponimod on neurodegeneration in demyelinating disease models remains to be fully elucidated. Histopathological analysis supported the imaging findings, revealing less pronounced demyelination, reduced inflammation, and enhanced axonal preservation in the siponimod-treated group. Immunohistochemical staining for markers of oxidative stress and neuronal damage demonstrated lower levels of these markers in the treatment group [1,2].

Literature Review

In this study, a murine model of demyelination was established using Theiler's Murine Encephalomyelitis Virus (TMEV). Animals were divided into two groups: a control group and a treatment group receiving siponimod. Neuroimaging was performed using high-resolution Magnetic Resonance Imaging (MRI) to assess brain and spinal cord structural changes, including demyelination and neurodegeneration markers [3]. Diffusion Tensor Imaging (DTI) was employed to investigate white matter integrity, while functional MRI (fMRI) assessed connectivity alterations. Analysis of the neuroimaging data revealed significant demyelination and neurodegeneration in the control group. Demyelination was evidenced by decreased myelin-sensitive signal and altered DTI metrics, indicating disrupted white matter microstructure. Moreover, fMRI connectivity analysis displayed reduced functional connectivity within key brain regions associated with demyelination. In contrast, the siponimod-treated group demonstrated a substantial attenuation of these neuroimaging markers. Notably, siponimod treatment resulted in preserved myelin-sensitive signal, improved DTI metrics, and enhanced fMRI connectivity patterns compared to the control group [4].

Discussion

The findings of this study provide compelling evidence for the potential neuroprotective effects of siponimod in a murine model of demyelination induced by TMEV. The observed attenuation of neurodegeneration-related imaging markers suggests that siponimod's immunomodulatory properties may extend to neuroprotection, mitigating axonal loss and preserving white matter integrity. These results align with clinical data showing siponimod's beneficial effects on relapse rates and disability progression in multiple sclerosis patients. While further mechanistic studies are needed to unravel the precise pathways underlying siponimod's neuroprotective effects, our study highlights its potential as a therapeutic agent in demyelinating disorders. The findings of this study suggest that siponimod exerts neuroprotective effects in a TME-induced demyelination model. By ameliorating imaging markers of neurodegeneration, siponimod appears to mitigate the pathological processes associated with demyelinating disorders. The observed improvements in DTI metrics and histopathological analyses suggest a potential mechanism involving both immunomodulation and direct neuroprotection [5,6].

Conclusion

This study demonstrates that siponimod exerts a beneficial impact on brain and spinal cord imaging markers of neurodegeneration in a murine model of demyelination caused by TMEV. The observed attenuation of demyelination-associated imaging markers suggests that siponimod's immunomodulatory effects might extend beyond its anti-inflammatory properties to confer neuroprotection. These findings contribute to our understanding of siponimod's mechanisms of action and its potential as a therapeutic strategy for neuroinflammatory demyelinating diseases, warranting further investigation in clinical settings. Siponimod, a sphingosine-1-phosphate receptor modulator, demonstrates significant potential as a therapeutic agent for neurodegenerative

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disorders like multiple sclerosis. The results of this study highlight its beneficial effects on brain and spinal cord imaging markers of neurodegeneration in a TME-induced demyelination model. Further research is warranted to elucidate the underlying mechanisms and to translate these findings into clinical applications for MS and related disorders.

Acknowledgement

None.

Conflict of Interest

None.

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