Remibrutinib Inhibits Neuroinflammation Driven by B cells and Myeloid Cells in EAE

Short title: Remibrutinib Inhibits Inflammation in EAE

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INTRODUCTION

Remibrutinib (LOU064) is a potent, highly selective, covalent Bruton tyrosine kinase (BTK) inhibitor with a promising preclinical and clinical profile for multiple sclerosis (MS) treatment.

OBJECTIVES

This study describes mechanism of action and efficacy of remibrutinib in experimental autoimmune encephalomyelitis (EAE) mouse models for MS.

METHODS

Two different EAE models in the C57BL/6 mouse that are induced by immunisation with human or rat myelin oligodendrocyte glycoprotein (HuMOG and RatMOG EAE) were used in the study. Target engagement in tissue, clinical disease activity, serum antibody levels, biomarkers, and central nervous system tissue transcriptome were analysed.

RESULTS

Remibrutinib inhibited B-cell dependent HuMOG EAE at daily oral doses of 3 and 30 mg/kg and strongly reduced neurological symptoms. *Ex vivo* MOG-specific T-cell recall response was inhibited, but not polyclonal T cell response, indicating selective B-cell inhibition. Remibrutinib did not reduce total immunoglobulin G antibody levels. At the efficacious dose of 30 mg/kg, remibrutinib showed strong BTK occupancy in the peripheral immune organs and in the brain of EAE mice. Remibrutinib also inhibited RatMOG EAE, indicating that myeloid cell and microglia inhibition contributes to its efficacy in MS. This is supported by anti-inflammatory effects detected in microglia, a single-cell RNA sequencing profiling of brain and spinal cord.

CONCLUSION

Remibrutinib exhibited dose-dependent efficacy in a B cell-driven EAE model. It revealed efficacy on clinical scores and anti-inflammatory effects by acting on myeloid cells and microglia. These findings support the view that remibrutinib may represent a novel treatment option for patients with MS.

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