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Remibrutinib inhibits neuroinflammation driven by B cells and myeloid cells in preclinical models of multiple sclerosis

B. Nuesslein-Hildesheim[1], E. Ferrero[1], C. Huck[1], P. Smith[2], D. Eichlisberger[1], B. Cenni[1]
[1]Novartis Institutes for Biomedical Research, Basel, Switzerland, [2]Connect Biopharma, San Diego, United States

Introduction: Bruton's tyrosine kinase (BTK) is a key signaling node in B-cell receptor and Fc receptor signaling. BTK inhibitors (BTKi) are an emerging oral treatment option for patients suffering from multiple sclerosis (MS). Remibrutinib (LOU064) is a potent, highly selective covalent BTKi with a promising preclinical and clinical profile for MS treatment.
Objective: To assess the 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 immunization with human or rat myelin oligodendrocyte glycoprotein (HuMOG and RatMOG EAE) were used in the study. Target engagement was assessed in tissue and clinical disease activity was determined. Serum antibody levels, biomarkers, as well as 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. Similarly, 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 a single-cell RNA sequencing of brain and spinal cord. In addition, remibrutinib significantly reduced neurofilament light chain serum levels.
Conclusions: Remibrutinib exhibited dose-dependent efficacy in a B cell-driven EAE model. In addition, 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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Barbara Nuesslein-Hildesheim, Enrico Ferrero, Catherine Huck, Denis Eichlisberger, and **Bruno Cenni** are employees of Novartis. **Paul Smith** is an employee of Connect Biopharma.