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Preclinical Studies

Abstract 5

Human Umbilical Cord Blood-Derived Cell Therapy Product, DUOC-01, Promotes Remyelination by Driving the Differentiation of Oligodendrocyte Progenitor Cells

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Introduction: DUOC-01 is a macrophage-like cell therapy product manufactured by culturing banked human umbilical cord blood cells under GMP conditions. Currently, the safety of DUOC-01 is being tested as a bridging therapy in children with demyelinating leukodystrophies undergoing unrelated donor umbilical cord blood transplantation after myeloablative conditioning. DUOC-01 protects against loss of function in several preclinical models with demyelinating conditions of the central nervous system, making it an attractive therapy for patients with multiple sclerosis (MS) who experience destruction of myelin sheaths as pathology of their disease. The mechanism by which DUOC-01 promotes remyelination and if it directly influences oligodendrocyte lineage cells is untested.

Objective: Using multiple systems (primary oligodendrocyte precursor cell [OPC] cultures, in vitro cerebellar slice cultures, and experimental autoimmune encephalomyelitis [EAE], a mouse model of MS), we examined how DUOC-01 influences numerous steps of pathology and recovery.

Methods: Using a brain slice culture, we added DUOC-01 to the lysophosphatidylcholine (LPC)-treated slices. We quantified myelinated axons by assessing percent co-localization of myelin basic protein and neurofilament in the control, LPC, and LPC+DUOC-01 groups. To test the DUOC-01 effect in the EAE model, we immunized C57BL/6 mice with myelin oligodendrocyte glycoprotein peptide (MOG_{35-55}) in complete Freund's adjuvant. To match clinical protocols, we incubated DUOC-01 in Ringer's lactate with hydrocortisone (HC) for 2 hours at room temperature. At the onset of EAE disease symptoms, we injected DUOC-01 into the cerebrospinal fluid by a single intracisterna magna injection, then recorded clinical scores daily for 2 weeks. To test if DUOC-01 could directly affect OPCs, we set up a primary OPC culture isolated from neonatal mice and added DUOC-01 treatment to the culture.

Results: In the cerebellar slice model, we demonstrated a higher number of myelinated neuron fibers in the DUOC-treated group compared with the LPC-treated group. In the EAE model, compared with mice injected with Ringer's or HC+Ringer's, mice injected with DUOC-01 derived clinical benefit with lower clinical scores. In the primary OPC culture, the DUOC-01 treatment drove the maturation of OPC to become myelin producing oligodendrocytes.

Discussion: Our data suggest that DUOC-01 could be beneficial in treating MS and other diverse neurological demyelinating conditions.