#1082: Siponimod in the Central Nervous System (CNS): Translational Evidence on its Penetration and Distribution

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Type

Abstract

Topic

MS and related disorders

Category

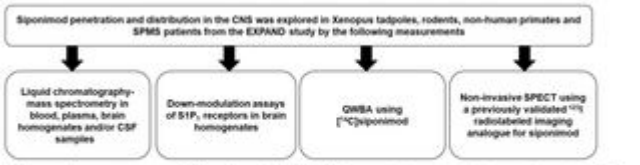
ePoster or Oral

Background and aims

Mechanism of action of siponimod is believed to involve, at low nM range, both sphingosine 1-phosphate (S1P) receptor subtype-1 ($S1P_1$)-dependent anti-inflammatory effects on pathogenic lymphocytes and glial cells in the CNS, and S1P receptor subtype-5 ($S1P_5$)-dependent pro-myelination effects on oligodendrocytes. This study consolidates translational evidence to establish penetration and distribution of siponimod in the CNS.

Methods

Siponimod CNS penetration/distribution was explored in Xenopus tadpoles, mice, rats, non-human primates (NHPs) and SPMS patients from the EXPAND study (Figure).



CNS, central nervous system; CSF, cerebrospinal fluid; QWBA, quantitative whole-body autoradiography; S1P, sphingosine-1-phosphate; SPECT, single-photon emission computed tomography; SPMS, secondary progressive multiple sclerosis

Figure. Study Methodology

Results

In tadpoles exposed to siponimod in swimming water, a dose-proportional increase in siponimod levels was obtained in brain homogenates. In mice, 10 days of siponimod-loaded diet produced dose-proportional steady-state blood siponimod levels, concomitant with 6- to 8-fold higher levels in brain-homogenates. Findings were similar in siponimod-treated rats (oral gavage, 7 days). In addition, siponimod cerebrospinal fluid (CSF)/plasma concentration ratio was 0.0025 and $S1P_1$ protein levels in brain-homogenates indicated a dose-dependent down-modulation of brain $S1P_1$ receptors. Quantitative whole-body autoradiography analysis in rats revealed highest siponimod-related radioactivity concentrations in the spinal cord, cerebellum (white matter), choroid plexus, medulla oblongata and corpus callosum. In NHPs, single photon emission computed tomography monitoring revealed siponimod distribution in the CNS with a brain/blood ratio of 6–8 as in mice. Of the EXPAND population (N=1,651), nine patients (five siponimod-treated) consented to CSF sampling at the end of treatment. Siponimod was detected in CSF of all siponimod-treated patients (sub-nM range).

Conclusion

Translational evidence from animal models and SPMS patients suggests penetration and distribution of siponimod in the CNS across species.

Disclosure

This study was funded by Novartis Pharma AG, Basel, Switzerland; a detailed disclosure from each author will be included in the oral/poster presentation.
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Affirmations

Authors agreement: I confirm, that all authors mentioned in the author block of this abstract have been informed about, and agreed to this submission. (I confirm)

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