Abstract 1380

Dual mode of action of siponimod in secondary progressive multiple sclerosis: A hypothesis based on the relevance of pharmacological properties

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Background

Siponimod, a potent and selective sphingosine 1-phosphate ($S1P_{1,5}$) receptor modulator, is the first oral disease-modifying therapy shown to reduce disability progression, cognitive decline, and total brain volume loss in secondary progressive multiple sclerosis (SPMS) patients. Recently presented data further suggest a favorable impact on more specific measures of neurodegeneration such as gray matter atrophy and myelin density assessed by magnetization transfer ratio. New preclinical insights further substantiate the dual mode of action (MoA) of siponimod demonstrating peripheral and central action targeting both inflammation and neurodegeneration.

Objectives

To propose a working hypothesis of a dual MoA for siponimod based on its unique specific pharmacological profile versus other S1P modulators.

Methods

Recent preclinical results with siponimod in pharmacokinetic/pharmacodynamic (PK/PD), mechanistic, and disease models were reviewed and placed in perspective.

Results

Preclinical data demonstrate that siponimod triggers $S1P_1$-dependent anti-inflammatory effects on pathogenic lymphocytes and glial cells in the central nervous system (CNS), and $S1P_5$-dependent promyelination effects on oligodendrocytes. Concomitant optimal $S1P_1$- and $S1P_5$-dependent effects are therefore required, in both blood and CNS compartments, for translation into clinical efficacy. Preclinical data indicate that the $S1P_1$- and $S1P_5$-dependent CNS effects follow non-classical pharmacology (“bell-shaped”), resulting in lowering of efficacy for agonists at supramaximal doses. This suggests an overall particularly complex drug dose-effect relationship. Recent preclinical PK/PD studies show that a CNS/blood drug exposure ratio ($_{CNS/blood}$DER) of ~6 allows siponimod to approach the top nadir of both $S1P_1$- and $S1P_5$-dependent dose-response curves in the blood and CNS compartments.

Hence, the $_{CNS/blood}$DER might be a key factor impacting therapeutic efficacy of an S1P-modulator. Fingolimod-phosphate has a higher $_{CNS/blood}$DER of 20–30, which might result in a potential therapeutic disadvantage compared to siponimod regarding $S1P_1$- and $S1P_5$-mediated CNS effects.

Conclusions

Preclinical findings show that siponimod has the pharmacological characteristics required for its dual $S1P_1$/$S1P_5$ MoA in both blood and CNS compartments, which may be of relevance for its clinical efficacy in SPMS. Translational and clinical studies are warranted to further validate this hypothesis.

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