Siponimod as a novel inhibitor of retinal angiogenesis: in vitro and in vivo evidence of therapeutic efficacy

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Abstract

Background and Purpose: S1P receptors control endothelial cell proliferation, migration, and survival. Evidence of the ability of S1P receptor modulators to influence multiple endothelial cell functions suggests their potential use for antiangiogenic effect. The main purpose of our study was to investigate the potential of siponimod for the inhibition of ocular angiogenesis in vitro and in vivo. Experimental Approach: We investigated the effects of siponimod on the metabolic activity (MTT assay), basal proliferation and growth factor induced proliferation (BrdU assay), and migration (transwell migration assay) of human umbilical vein endothelial cells (HUVEC) and retinal microvascular endothelial cells (HRMEC). The effects of siponimod on HRMEC monolayer integrity, and barrier function under basal conditions and TNF-α induced disruption were assessed using the trans-endothelial electrical resistance (TEER) and FITC-dextran permeability assays. Siponimod’s effect on TNF-α induced claudin-5 distribution in HRMEC was investigated using immunofluorescence. Finally, the effect of siponimod on ocular neovascularization in vivo was assessed using suture-induced corneal neovascularization in albino rabbits. Key Results: Siponimod did not affect endothelial cell proliferation or metabolic activity, but significantly inhibited endothelial cell migration, increased HRMEC barrier integrity, and reduced TNF-α induced barrier disruption. Siponimod also protected against TNF-α induced disruption of claudin-5 in HRMEC. These actions are mainly mediated by SIPRI receptor modulation. Finally, siponimod prevented the progression of suture-induced corneal neovascularization in albino rabbits. Conclusion and Implications: The effects of siponimod on various processes known to be involved in angiogenesis support its therapeutic potential in disorders associated with ocular neovascularization.

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Figure 1

Figure 2
Figure 3
**Figure 4**

**Figure 5**
Figure 6

Figure 7
Figure 8