

# Medical Update Memo

May 10, 2010

## Fingolimod (FTY720) Enhances Remyelination Following Demyelination of Organotypic Cerebellar Slices

### Summary

The myelin sheath found around neurons is essential for the proper function of the nervous system. Demyelination is the loss of this sheath and remyelination is critical to restore proper neuronal function. Canadian researchers (Miron VE, Ludwin SK, Darlington PJ, Jarjour AA, Soliven B, Kennedy TE, Antel JP.) studied the impact of fingolimod (a new therapy for MS) on mouse cell culture. The preliminary data suggested that fingolimod could be involved in enhancing the remyelination process in the mammalian brain.

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### Details

Remyelination, which occurs subsequent to demyelination, contributes to functional recovery and is mediated by oligodendrocyte progenitor cells (OPCs) that have differentiated into myelinating cells. Therapeutics that impact remyelination in the CNS could be critical determinants of long-term functional outcome in multiple sclerosis (MS). Fingolimod is a S1P receptor modulator in MS clinical trials due to systemic anti-inflammatory properties, yet may impact cells within the CNS by crossing the blood-brain barrier. Previous studies using isolated dissociated cultures indicate that neural cells express S1P receptors and respond to receptor engagement. Researchers' objective was to assess the effects of fingolimod on myelin-related processes within a multicellular

environment that maintains physiological cell-cell interactions, using organotypic cerebellar slice cultures. Fingolimod treatment had no impact on myelin under basal conditions. Fingolimod treatment subsequent to lysolecithin-induced demyelination enhanced remyelination and process extension by OPCs and mature oligodendrocytes, while increasing microglia numbers and immunoreactivity for the astrocytic marker glial fibrillary acidic protein. The number of phagocytosing microglia was not increased by fingolimod. Using S1P receptor specific agonists and antagonists, it was determined that fingolimod-induced effects on remyelination and astrogliosis were mediated primarily through S1P3 and S1P5, whereas enhanced microgliosis was mediated through S1P1 and S1P5. Taken together, these data demonstrate that fingolimod modulates multiple neuroglial cell responses, resulting in enhanced remyelination in organotypic slice cultures that maintain the complex cellular interactions of the mammalian brain.

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