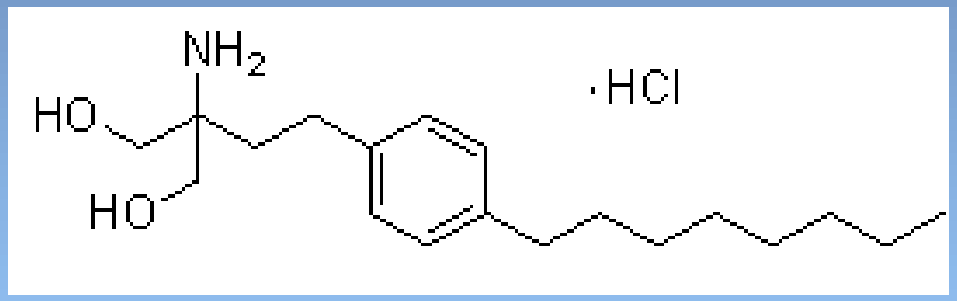
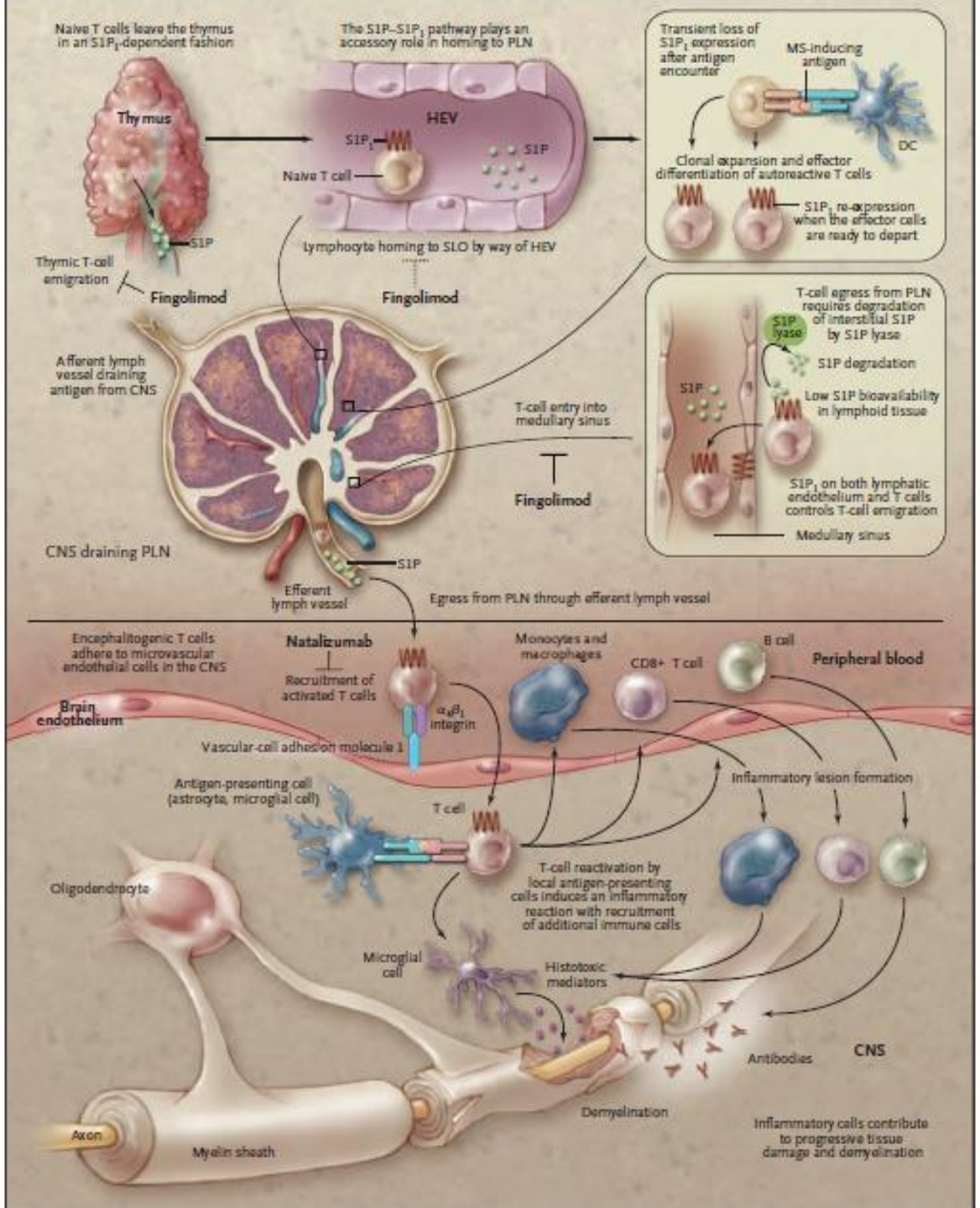
Fingolimod (Gilenya, Novartis)
FTY720



Ella Shaviv
Sackler SOM, MS4

Mechanism of Action

- sphingosine-1-phosphate receptor modulator
- preventing lymphocyte egress from lymph nodes
- reverses the effects of BCR-ABL kinase by activates phosphatase 2A (PP2A)
- activating PKC


Naive T cells leave the thymus in an $S1P_1$-dependent fashion
The S1P–$S1P_1$ pathway plays an accessory role in homing to PLN
Thymus
HEV
$S1P_1$
S1P
Naive T cell
Thymic T-cell emigration
Fingolimod
Lymphocyte homing to SLO by way of HEV
Fingolimod
Transient loss of $S1P_1$ expression after antigen encounter
MS-inducing antigen
DC
Clonal expansion and effector differentiation of autoreactive T cells
$S1P_1$ re-expression when the effector cells are ready to depart
Afferent lymph vessel draining antigen from CNS
T-cell entry into medullary sinus
Fingolimod
T-cell egress from PLN requires degradation of interstitial S1P by S1P lyase
S1P lyase
S1P degradation
Low S1P bioavailability in lymphoid tissue
$S1P_1$ on both lymphatic endothelium and T cells controls T-cell emigration
Medullary sinus
CNS draining PLN
Efferent lymph vessel
Egress from PLN through efferent lymph vessel
Encephalitogenic T cells adhere to microvascular endothelial cells in the CNS
Natalizumab
Recruitment of activated T cells
$\alpha_4\beta_1$ integrin
Vascular-cell adhesion molecule 1
Brain endothelium
Monocytes and macrophages
CD8+ T cell
B cell
Peripheral blood
Antigen-presenting cell (astrocyte, microglial cell)
T cell
Inflammatory lesion formation
Oligodendrocyte
T-cell reactivation by local antigen-presenting cells induces an inflammatory reaction with recruitment of additional immune cells
Microglial cell
Histotoxic mediators
Antibodies
CNS
Demyelination
Axon
Myelin sheath
Inflammatory cells contribute to progressive tissue damage and demyelination

Indications / Dosing

- Approved Sept 2010 for Relapsing MS:
  - Reduces number of MS flares and slows disability
- 0.5 mg PO qd, with or without food

- Interactions:
  - blood levels of fingolimod are increased when combined with ketoconazole
  - additional 15% reduction of heart rate with Atenolol

Adverse Affects

- nasopharyngitis,
- Dyspnea/cough
- headache, back pain
- diarrhea,
- Nausea,
- posterior reversible encephalopathy syndrome
- **Bradycardia** and atrioventricular conduction block at the time of fingolimod initiation,
- **macular edema**,
- elevated liver-enzyme levels,
- mild hypertension
- modest decrease in the forced expiratory volume in 1 second of initiation
- **Infection -** Live attenuated vaccines should not be administered during and for 2 months after fingolimod treatment because of the risk of infection
- Skin cancer

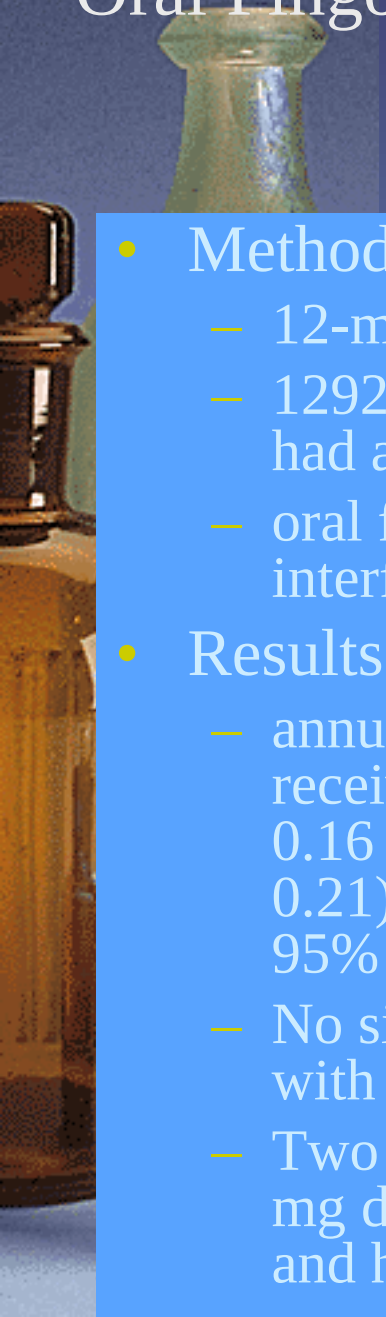
Oral Fingolimod (FTY720) for Relapsing Multiple Sclerosis

- Methods:
  - 281 patients to receive oral fingolimod, at a dose of 1.25 mg or 5.0 mg, or a placebo once daily
  - Double blind
  - Clinical and MRI 6m followup
- Results:
  - The median number of lesions lower with 1.25 mg of fingolimod ($P<0.001$) and 5.0 mg ($P = 0.006$) than with placebo
  - annualized relapse rate was 0.77 in the placebo group, as compared with 0.35 with 1.25 mg of fingolimod ($P = 0.009$) and 0.36 with 5.0 mg of fingolimod ($P = 0.01$)
  - both measures decreased in patients who switched from placebo to fingolimod

A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis

- Methods:
  - 24-month, double-blind, randomized study
  - 1272 patients with relapsing–remitting multiple sclerosis, were 18 to 55 years of age, had a score of 0 to 5.5 on the Expanded Disability Status Scale
  - oral fingolimod at a dose of 0.5 mg or 1.25 mg daily or placebo
- Results:
  - The annualized relapse rate was 0.18 with 0.5 mg of fingolimod, 0.16 with 1.25 mg of fingolimod, and 0.40 with placebo ($P<0.001$ for either dose vs. placebo)
  - significantly reduced the risk of disability progression over the 24-month period (hazard ratio, 0.70 and 0.68, respectively; $P = 0.02$ vs. placebo
  - cumulative probability of disability progression (confirmed after 3 months) was 17.7% with 0.5 mg of fingolimod, 16.6% with 1.25 mg of fingolimod, and 24.1% with placebo
  - Both fingolimod doses were superior to placebo with regard to MRIrelated Measures ($P<0.001$)

Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis



- Methods:
  - 12-month, double-blind, double-dummy study
  - 1292 patients with relapsing–remitting multiple sclerosis who had a recent history of at least one relapse
  - oral fingolimod at a daily dose of either 1.25 or 0.5 mg or IM interferon beta-1a weekly dose of 30 μg
- Results:
  - annualized relapse rate was significantly lower in both groups receiving fingolimod — 0.20 (95% confidence interval [CI], 0.16 to 0.26) in the 1.25-mg group and 0.16 (95% CI, 0.12 to 0.21) in the 0.5-mg group — than in the interferon group (0.33; 95% CI, 0.26 to 0.42; $P<0.001$ for both comparisons)
  - No significant differences were seen among the study groups with respect to progression of disability
  - Two fatal infections occurred in the group that received the 1.25-mg dose of fingolimod: disseminated primary varicella zoster and herpes simplex encephalitis

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