Fingolimod

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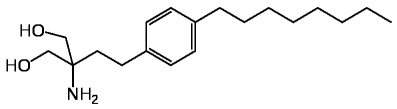

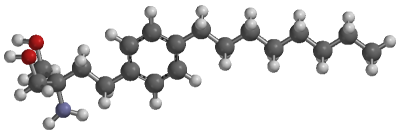

Systematic (IUPAC) name	
2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol	
Identifiers	
CAS number	162359-55-9 [1]
ATC code	L04 AA27 [2]
PubChem	CID 107970 [3]
ChemSpider	97087 [4] ✓
ChEMBL	CHEMBL314854 [5] ✓
Chemical data	
Formula	$C_{19}H_{33}NO_2$
Mol. mass	307.471 g/mol
SMILES	eMolecules [6] & PubChem [7]
Therapeutic considerations	
Licence data	US FDA: link [8]
Pregnancy cat.	C(US)
Legal status	-only (US)
Routes	Oral
✓ **(what is this?) (verify)** [9]	

Fingolimod (rINN, codenamed **FTY720**) is an immunosuppressive drug. It is derived from the myriocin (ISP-1) metabolite of the fungus *Isaria sinclairii*. It is a structural analogue of sphingosine and gets phosphorylated by sphingosine kinases in the cell (most importantly sphingosine kinase 2).[10] [11] [12] The molecular biology of phospho-fingolimod is thought to lie in its activity at one of the five sphingosine-1-phosphate receptors, S1PR1.[13] It can sequester lymphocytes in lymph nodes, preventing them from moving to the central nervous system for auto-immune responses in multiple sclerosis and was originally proposed as a anti-rejection medication indicated post-transplantation. It has been reported to stimulate the repair process of glial cells and precursor cells after injury.[14] Fingolimod has also been reported to be a cannabinoid receptor antagonist,[15] a cPLA2 inhibitor [16] and a

ceramide synthase inhibitor.[17]

On September 22, 2010, fingolimod became the first oral disease-modifying drug approved by the Food and Drug Administration as Gilenya[18] to reduce relapses and delay disability progression in patients with relapsing forms of multiple sclerosis.[19] The manufacturer announced on March 10, 2011 that it had received a notice of compliance from Health Canada and that the drug would be available April 1, 2011 at pharmacies.[20] [21]

History

First synthesized in 1992, fingolimod was derived from an immunosuppressive natural product, myriocin (ISP-I) through chemical modification. Myriocin was isolated from the culture broth a type of entomopathogenic fungi (*Isaria sinclairii*) that was an eternal youth nostrum in traditional Chinese medicine.[22] Showing positive results in both *in vitro* (mixed lymphocyte reaction) and *in vivo* screening (prolonging rat skin graft survival time), myriocin was modified through a series of steps to yield fingolimod, code named at the time FTY720. [23]

Structure activity relationship (SAR) studies on myriocin homologs and partially synthetic derivatives showed that the configuration at the carbon bearing the 3-hydroxy group or the 14-ketone, the 6-double bond, and the 4-hydroxy group were not important for its activity and simplification of the structure of ISP-I was done in an attempt to reduce toxicity and improve drugability [24]

Elimination of side chain functionalities and removal of chiral centers was part of the simplification process and an intermediate compound (ISP-I-28) with the carboxylic acid of myriocin transformed to a hydroxymethyl group was generated. ISP-I-28 was found to be less toxic and more effective at lenghtening rat skin allograft time than ISP-1.

Clinical trials

Organ transplant

In a previous phase III clinical trial of kidney transplantation, fingolimod was found to be no better than the existing standard of care.[25] [26] The fingolimod is studied in the human models in vitro and animal kidney transplantation.[27] [26] [28] [28]

Multiple sclerosis

In two Phase III clinical trials, fingolimod reduced the rate of relapses in relapsing-remitting multiple sclerosis by over half compared both to placebo *and to the active comparator interferon beta-1a*.[29]

A double-blind randomized control trial comparing fingolimod to placebo[30] found the drug reduced the annualized frequency of relapses to 0.18 relapses per year at 0.5 mg/day or 0.16 relapses per year at 1.25 mg/day, compared to 0.40 relapses per year for those patients taking the placebo. The probability of disease progression at 24 month followup was lower in the fingolimod groups compared to placebo (hazard ratio 0.70 at 0.5 mg and 0.68 at 1.25 mg). Fingolimod patients also had better results according to MRI imaging of new or enlarged lesions at 24 month followup. Side effects leading to discontinuation of the study drug were more common in the higher dose group (14.2% of patients) than at the lower dose (7.5%) or placebo (7.7%). Serious adverse events in the fingolimod group included bradycardia, relapse, and basal-cell carcinoma. Seven episodes of bradycardia occurred during the monitoring period after administration of the first dose, and were asymptomatic in six of these cases. There was a higher rate of lower respiratory tract infections (including bronchitis and pneumonia) in the fingolimod groups (9.6% at 0.5 mg, 11.4% at 1.5 mg) than the placebo group (6.0%). Other adverse events reported on the study drug included macular edema, malignant neoplasms, and laboratory abnormalities.[31]

Side effects

Fingolimod has been associated with potentially fatal infections, bradycardia, skin cancer and, recently, a case of haemorrhaging focal encephalitis, an inflammation of the brain with bleeding. Two subjects died: one due to brain herpes infection, second one due to zoster. It is unclear whether the drug was responsible for the events.[32]

The most common side effects of fingolimod have been head colds, headache, and fatigue. But there have also been a few cases of skin cancer, which has also been reported in patients taking natalizumab (Tysabri), an approved MS drug.[33]

Chemical synthesis

Several studies have described the synthesis of fingolimod and analogs.[34] [35]

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