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Mini Review

Fingolimod (FTY720), the Sphingosine 1-Phosphate Receptor Modulator, as a New Therapeutic Drug in Multiple Sclerosis

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FTY720 (Fingolimod) is a first-in-class sphingosine 1-phosphate (S1P) receptor modulator that inhibits S1P-dependent lymphocyte egress from secondary lymphoid organs. Oral administration of FTY720 shows a superior efficacy compared to interferon (IFN)-β in relapsing remitting multiple sclerosis (MS), the most common inflammatory disorder of the central nervous system (CNS) and in experimental autoimmune encephalomyelitis (EAE), a CD4 T cell-dependent animal model for MS. FTY720 is a structural analogue of sphingosine and is rapidly converted to the (*S*)-enantiomer of FTY720-phosphate [(*S*)-FTY720-P)] by sphingosine kinases. (*S*)-FTY720-P binds 4 types of S1P receptors ($S1P_1$, $S1P_3$, $S1P_4$, and $S1P_5$), induces internalization and degradation of lymphocytic $S1P_1$, and inhibits S1P responsiveness of lymphocytes. Consequently, (*S*)-FTY720-P acts as a functional antagonist at $S1P_1$ thereby inhibiting S1P-$S1P_1$ axis-mediated lymphocyte egress from secondary lymphoid organs. Based on this mechanism, FTY720 sequesters myelin antigen-specific CD4 T cells including interleukin 17-expressing helper T cells (Th17 cells) and IFN-γ-expressing type 1 helper T cells (Th1 cells) into the lymph nodes, and reduces the infiltration of these Th cells into the CNS in mouse EAE. Since FTY720 was approved by the United States Food and Drug Administration in September 2010 as a first-line treatment for relapsing remitting MS, it is presumed that oral FTY720 provides a new therapeutic approach for MS.

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Introduction: Discovery of FTY720

About twenty years ago, we isolated a series of immunomodulating natural products, (2*S*, 3*R*, 4*R*)-(*E*)-2-amino-3, 4-dihydroxy-2-(hydroxymethyl)-14-oxoeicos-6-enoic acid, (ISP-I = myriocin = thermozymocidin) and mycestericins A-G from culture broths of *Isaria sinclairii* and *Mycelia sterilia* [1]. Extensive modifications of ISP-I were conducted and simplification of the structure of ISP-I including removal of the side chain functionalities as well as elimination of chiral centers led to a novel compound, 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol (FTY720, fingolimod) with more potent immunomodulating activity and less toxicity compared with ISP-I [2, 3]. Although ISP-I inhibits interleukin (IL)-2-dependent proliferation of mouse CI'LL-2 cells by inhibiting serine palmitoyl transferase, the first enzyme in sphingolipid biosynthesis, FTY720 showed no effect on serine palmitoyl transferase, suggesting that FTY720 possesses a new mechanism of action distinct from ISP-I [4].

FTY720 at an oral dose of 0.1 mg/kg or higher significantly prolongs allograft survival and shows a synergistic effect in combination with calcineurin inhibitors (cyclosporine A and tacrolimus) in experimental skin, cardiac and renal allotransplantation models [4, 5]. Moreover, oral administration of FTY720 is highly effective in various autoimmune disease models including experimental autoimmune encephalomyelitis (EAE), adjuvant- or collagen-induced arthritis in rats and mice, and lupus nephritis in MRL/*lpr* mice [4, 6, 7]. Unlike calcineurin inhibitors, FTY720 does not impair lymphocyte function including T cell activation and production of IL-2 and interferon (IFN)-γ by antigen stimulation [8-10].

FTY720 sequesters circulating lymphocytes into the SLO

A striking feature of FTY720 is the induction of a marked decrease in the number of peripheral blood lymphocytes (T cells and B cells) at doses that show an immunomodulating activity [5, 8]. To clarify the mechanism of lymphocyte reduction by FTY720, we analyzed the lymphocyte distribution in the blood, lymph and secondary lymphoid organs (SLO: peripheral lymph nodes, mesenteric lymph nodes, and Peyer's patches) after FTY720 administration [8]. When FTY720 (0.1 and 1 mg/kg) was orally administered to rats, the number of lymphocytes was decreased markedly in the peripheral blood and thoracic duct lymph whereas that in the SLO was increased significantly, and transfused fluorescein-labeled lymphocytes were accumulated into the SLO by FTY720 [8]. These data suggest that FTY720 induces sequestration of circulating mature lymphocytes into the SLO thereby decreasing the number of lymphocytes in the peripheral blood and lymph. Consequently, the sequestration of circulating mature lymphocytes into the SLO is presumed to be the main mechanism of immunomodulating activity of FTY-720.

Phosphorylated FTY720 acts as a functional antagonist at $S1P_1$ receptor

By reverse pharmacological approaches to clarify the mechanism of action of FTY720, it has been demonstrated that like sphingosine, FTY720 is a substrate for sphingosine kinases and that a phosphorylated form of FTY720 (FTY720-P) acts as an agonist of sphingosine 1-phosphate (S1P) receptors [11, 12]. S1P, a pleiotropic lysophospholipid mediator is converted primarily by the phosphorylation of sphingosine by sphingosine kinases, binds to five related G-protein-coupled receptors ($S1P_1$, $S1P_2$, $S1P_3$, $S1P_4$, and $S1P_5$) with nanomolar (nM) affinities, and stimulates multiple signaling pathways resulting in calcium mobilization from intracellular stores, polymerization of actin, chemotaxis/migration, and escape from apoptosis.

After oral FTY720 administration, only the (*S*)-enantiomer of FTY720-P [(*S*)-FTY720-P] was found in the blood and the blood concentration of (*S*)-FTY720-P was 2 to 6 times higher than that of FTY720. The (*S*)-FTY720-P can bind to four types of S1P receptors ($S1P_1$, $S1P_3$, $S1P_4$, and $S1P_5$) with high affinity (at sub nano-molar concentrations) [13]. On the other hand, the (*R*)-enantiomer of FTY720-P shows lower affinity at S1P receptors (about 100-fold weaker) than the (*S*)-enantiomer, and FTY720 up to 10000 nM does not bind S1P receptors [13]. (*S*)-FTY-720-P shows agonist activity for $S1P_1$ and subsequently induces long-term internalization and degradation of $S1P_1$ [4, 14, 15]. The pretreatment with (*S*)-FTY720-P effectively inhibits the migration of CD4 T cells toward S1P, suggesting that (*S*)-FTY-720-P inhibits S1P responsiveness by internalization and degradation of $S1P_1$ and acts as a functional antagonist at lymphocytic $S1P_1$ [14, 15].

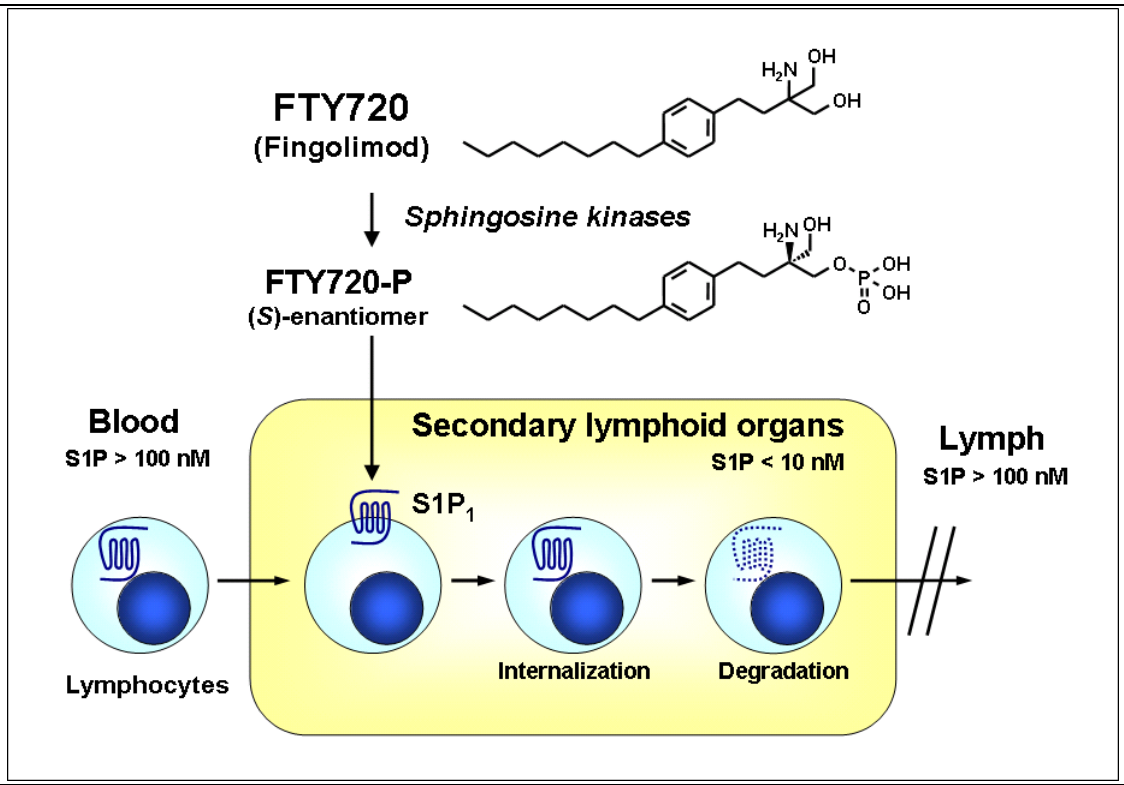

Fig. 1

FTY720-P converted from FTY720 acts as a functional antagonist at lymphocytic $S1P_1$ by internalization and degradation of the receptor, and inhibits S1P-$S1P_1$ axis-mediated lymphocyte egress from the SLO.

FTY720 inhibits S1P-$S1P_1$ axis-mediated lymphocytes egress from the SLO

Circulation of mature lymphocytes among the SLO, lymph, and blood plays a central role in the establishment of the immune response to foreign antigens. Homing of lymphocytes from blood into the SLO beyond high endothelial venules is highly dependent on the interaction between the CC-chemokine receptor 7 (CCR7) on lymphocytes and its ligands (CCL19 and CCL21). On the other hand, it is clarified that S1P and $S1P_1$ plays an essential role in lymphocyte egress from the SLO to lymph because mature T cells are unable to exit from the SLO and there are no T cells in periphery in mice whose hematopoietic cells lack $S1P_1$ [4, 16, 17]. Furthermore, FTY720 treatment down-regulates $S1P_1$, creating a temporary pharmacological $S1P_1$-null state in lymphocytes, providing an explanation for the mechanism of FTY720-induced lymphocyte sequestration [4, 16, 17].

The $S1P_1$ surface expression on lymphocytes is highly dependent on the extracellular concentration of S1P. The expression of lymphocytic $S1P_1$ is down-regulated in the blood, up-regulated in the SLO, and down-regulated again in the lymph because the concentration of S1P is relatively higher (100-400 nM) in blood and lymph whereas S1P in the SLO is maintained at low concentration (less than 10 nM) by S1P lyase. Thus, it is proposed that cyclical modulation of $S1P_1$ surface expression on circulating lymphocytes by S1P contributes to establishing their transit time in the SLO [18]. Based on these results, it is presumed that (*S*)-FTY720-P converted from FTY720 acts as a functional antagonist at lymphocytic $S1P_1$ by internalization and degradation of the receptor and shows immunomodulating activity by inhibition of S1P-$S1P_1$ axis-mediated lymphocyte egress from the SLO (Fig.1).

Therapeutic effects of FTY720 on EAE in mice

It is well known that experimental autoimmune encephalomyelitis (EAE) is a CD4 T cell-dependent animal model for human multiple sclerosis (MS). Prophylactic treatment with FTY720 almost completely prevented the development of EAE and FTY720 showed therapeutic effects on EAE induced by immunization with myelin proteolipid protein

(PLP) in SJL/J mice [6]. We directly compared the therapeutic effects of FTY720 and recombinant mouse IFN-β (rm-IFN-β) on relapse and progression of EAE in mice [19]. When FTY720 at oral doses of 0.1 and 0.3 mg/kg was administered daily after establishment of EAE induced by PLP in SJL/J mice, relapse of EAE was significantly inhibited during administration period (Fig. 2). Subcutaneous injection of rm-IFN-β (10000 IU/mouse) also inhibited the relapse of EAE at early period; however EAE was relapsed in all the mice within administration period (Fig. 2). Therapeutic administration of FTY720 (0.03 to 1 mg/kg) significantly improved the symptoms of chronic EAE induced by myelin oligodendrocyte glycoprotein (MOG) in C57BL/6 mice whereas rm-IFN-β (10000 IU/mouse) showed no clear effect. These results indicate that FTY720 shows superior efficacy as compared with rm-IFN-β in mouse EAE.

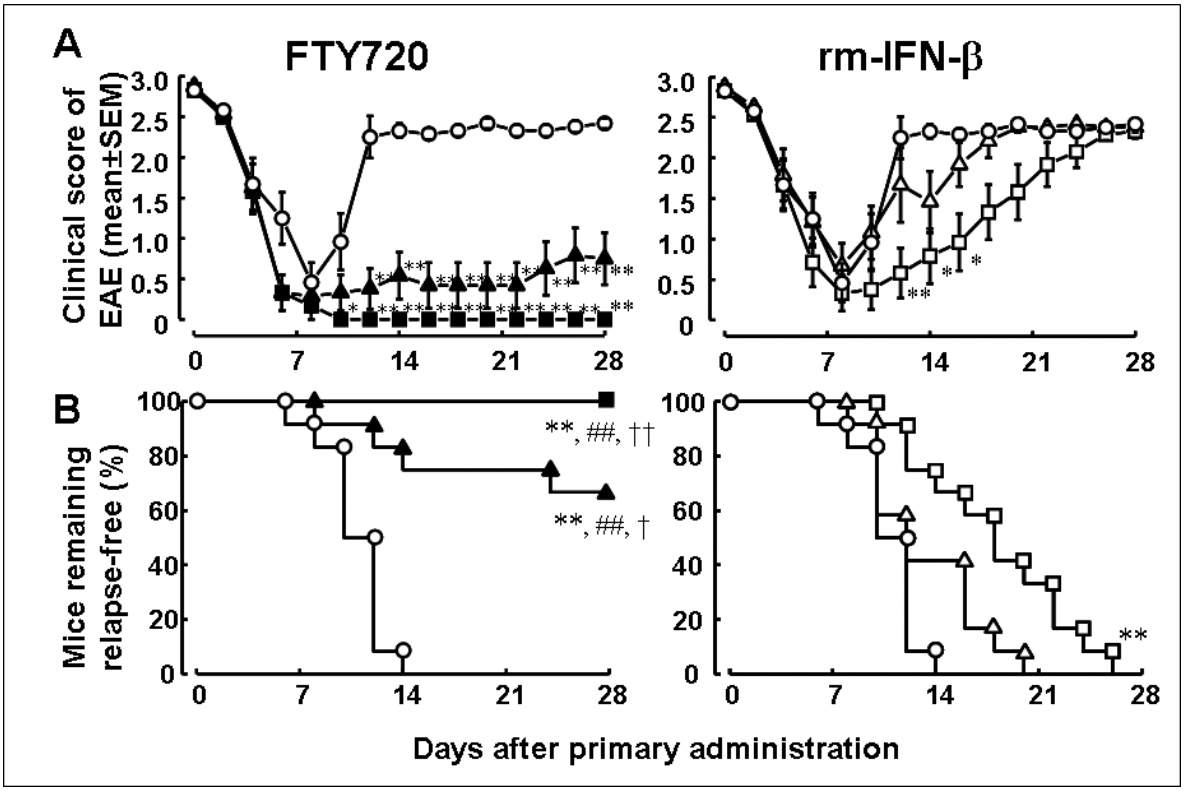

Fig. 2 Therapeutic effects of FTY720 and rm-IFN-β on relapsing remitting EAE induced by $PLP_{139-151}$ in SJL/J mice.

SJL/J mice were immunized with $PLP1_{39-151}$ (50 μg/mouse) and Freund's complete adjuvant. EAE-developed mice were divided into 5 groups on day 15 after the immunization. FTY720 were administered orally every day for 28 days: ○, control (vehicle); ▲, FTY720 0.1 mg/kg; ■, FTY720 0.3 mg/kg. rm-IFN-β were administered subcutaneously every other day for 28 days: ○, control; △, rm-IFN-β 3,000 IU/mouse; □, rm-IFN-β 10,000 IU/mouse. (A). Clinical scores are expressed as the mean ± S.E.M. of 12 mice. Statistical differences in EAE scores were calculated by Steel's test (*: $p<0.05$, **: $p<0.01$ versus vehicle-treated control group). (B) Results are expressed as the proportion of mice remaining relapse-free in total 12 mice. Statistical differences were calculated by generalized Wilcoxon test adjusted by Holm's multiple comparison test (**: $p<0.01$ versus vehicle-treated control, ##: $p<0.01$ versus rm-IFN-β 3,000 IU/mouse, †: $p<0.05$, ††: $p<0.01$ versus rm-IFN-β 10,000 IU/mouse). (Adapted from Chiba et al.[19])

Recent studies reveal that IL-17-expressing helper T cells (Th17 cells) as well as IFN-γ-expressing type 1 helper T cells (Th1 cells) play a pathological role in mouse EAE. Therapeutic treatment with FTY720 markedly reduced the area of demyelination and infiltration of CD4 T cells including PLP-specific Th17 and Th1 cells in the spinal cord of EAE mice induced by immunization with PLP [4, 6, 19] (Fig. 3). On the contrary, FTY720 increased the frequency of PLP-specific Th17 and Th1 cells in the inguinal lymph nods, suggesting inhibition of egress of myelin antigen-specific Th cells from the draining lymph

nodes [19] (Fig. 3). Indeed, Th17 and Th1 cells can migrate toward 10 nM S1P *in vitro* and the pretreatment with (*S*)-FTY720-P almost completely inhibited the migration of these Th cells toward S1P, implying that the egress of these Th cells from lymph nodes depends on S1P-$S1P_1$ axis [20]. Based on these results, the ameliorating effects of FTY720 on EAE are likely due to reduction of infiltration of myelin antigen-specific Th17 and Th1 cells into the central nervous system (CNS).

Therapeutic effects of FTY720 in relapsing remitting MS

The first clinical evidence that FTY720 has the therapeutic benefits in MS was provided in a 6-month, placebo-controlled Phase II trial involving 281 patients with relapsing remitting MS (RRMS) [21]. Patients receiving FTY720 at an oral dose of 1.25 mg or 5.0 mg daily had a significant lower median total number of gadolinium-enhancing lesions (the primary end point) on magnetic resonance imaging (MRI) than those receiving placebo. The annualized relapse rates in groups given 1.25 mg and 5.0 mg of FTY720 were 0.35 and 0.36, respectively and were significantly lower than that in the placebo group (0.77). By extension study for additional 6 months, the number of gadolinium-enhanced lesions and relapse rates remained low in groups given FTY720 and both measures decreased in patients who switched from placebo to FTY720.

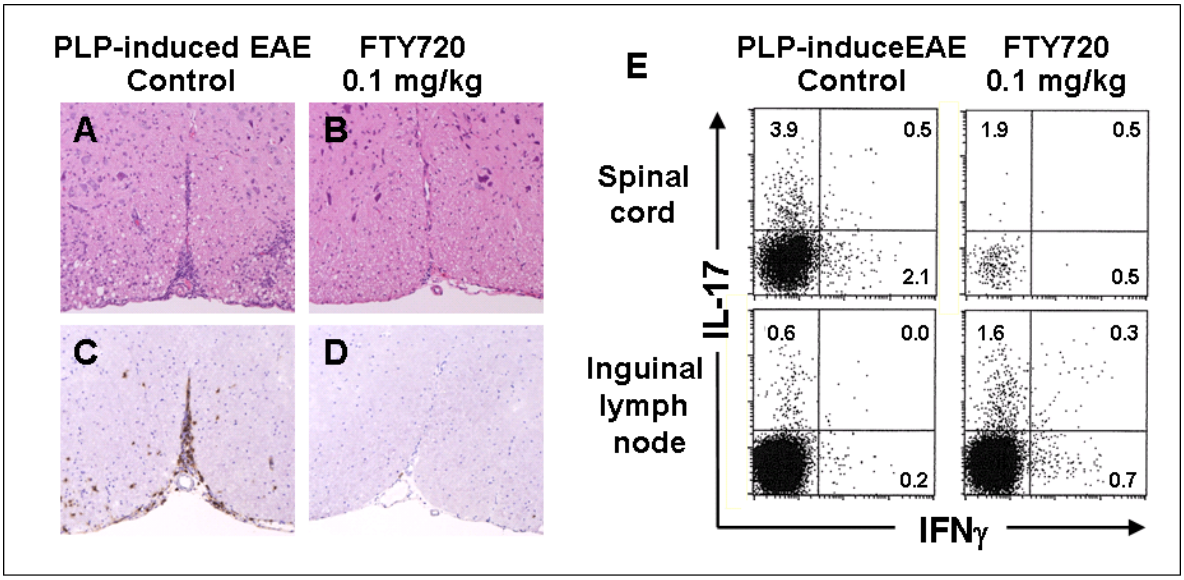

Fig. 3

Therapeutic administration of FT720 decreases the demyelination and infiltration of CD4 T cells including PLP-specific Th1 and Th17 cells in the spinal cords of EAE mice immunized with PLP.

SJL/J mice were immunized with $PLP1_{39\text{-}151}$ (50 μg/mouse) and Freund's complete adjuvant. EAE-developed mice were administered FTY720 at an oral dose of 0.1 mg/kg therapeutically for 28 days. On the next day of the final administration, the spinal cords were obtained and were stained with hematoxylin and eosin: (A) control, (B) FTY720 0.1 mg/kg. Immunohistochemical staining of the spinal cords was performed by using anti-mouse CD4 mAb: (C) control, (D) FTY720 0.1 mg/kg. (E) lymphocytes prepared from the spinal cords or inguinal lymph nodes of EAE mice were cultured for 72 h in the presence of $PLP_{139\text{-}151}$ (50 μg/ml). After the culture, intracellular cytokine staining was performed by using anti-CD4, anti-IL-17, and anti-IFN-γ mAbs. (Adapted from Chiba et al.[19])

In FTY720-treated MS patients, the number of IL-17-expressing CD4 T cells were reduced by >95% in the peripheral blood suggesting that FTY720 inhibits egress of Th17 cells from the SLO and reduces the infiltration of Th17 cells into the CNS [22, 23]. In addition, FTY720 primarily reduced the numbers of $CCR7^+$ $CD45RA^+$ naïve T cells and $CCR7^+$ $CD45RA^-$ central memory T cells in the blood in MS patients, because these T cells express the homing receptor CCR7, recirculate through the lymph nodes, and can be sequestered into the lymph nodes by FTY720. In contrast, $CCR7^-$ $CD45RA^-$ and $CCR7^-$ $CD45RA^+$ effector memory T cell subsets are not sequestered into the SLO and are remained in the blood when

FTY720 is administered. These results suggest that FTY720 effectively inhibits infiltration of pathogenic CD4 T cells including Th 17 cells into the CNS in MS patients whereas FTY720 does not affect the function of effector memory T cells that play an important role in the prevention of infection.

Table 1 Efficacy of FTY720 in the FREEDOMS and TRANSFORMS studies

FREEDOMS study (24 months)			
	FTY720 0.5 mg	FTY720 1.25 mg	Placebo
Annualized relapse rate	0.18 n=425 p<0.001	0.16 n=429 p<0.001	0.40 n=418
Median (mean) number of New or enlarged T2 lesions	0.0(2.5) n=370 p<0.001	0.0(2.5) n=337 p<0.001	5.0(9.8) n=339
TRANSFORMS study (12 months)			
	FTY720 0.5 mg	FTY720 1.25 mg	IFN-β1a
Annualized relapse rate	0.16 n=429 p<0.001	0.20 n=420 p<0.001	0.33 n=431
Median (mean) number of New or enlarged T2 lesions	0.0(1.7) n=380 p=0.004	1.0(1.5) n=356 p<0.001	1.0(2.6) n=365

FTY720 was evaluated in a 24-month, double blind Phase III study (FREEDOMS study), involving 1272 patients with RRMS [24] (Table 1). The patients were randomized to receive a daily oral dose of FTY720 at 0.5 mg or 1.25 mg, or placebo. The annualized relapse rates in groups given 0.5 mg and 1.25 mg of FTY720 were 0.18 and 0.16, respectively and were significantly lower than that in the placebo group (0.40). FTY720 at 0.5 mg and 1.25 mg significantly reduced the risk of disability progression over 24-month period. The cumulative probability of disability progression confirmed after 3 months was 17.7% with 0.5 mg FTY720, 16.6% with 1.25 mg FTY720, and 24.1% with placebo. FTY720 at 0.5 mg and 1.25 mg showed improved effects compared with placebo with regard to the MRI-related measures (number of new or enlarged lesions on T2-weightend images, gadolinium-enhanced lesions, and brain-volume loss).

FTY720 was also evaluated in a 12-month, double blind, double dummy Phase III study (TRANSFORMS study) involving 1292 patients with RRMS, comparing FTY720 with IFN-β1a, an established therapy for MS [25] (Table 1). Patients were randomized to receive a daily dose of 0.5 mg or 1.25 mg FTY720 orally, or a weekly intramuscular injection of IFN-β1a. The annualized relapse rates in groups given FTY720 0.5 mg and 1.25 mg were 0.16 and 0.20 respectively, and were significantly lower than that in the group receiving IFN-β1a (0.33). FTY720 at 0.5 mg and 1.25 mg showed improved effects compared with IFN-β1a with regard to MRI-related measures. These Phase III studies demonstrated that oral FTY720 had superior efficacy compared with intramuscular IFN-β1a and placebo with regard to reducing the rate of relapse and MRI-related measures of inflammatory lesion activity. Since FTY720 was approved by the United States Food and Drug Administration in September 2010 as a first-line treatment for RRMS, it is presumed that oral FTY720 provides a new therapeutic approach for MS.

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