Oral Disease Modifying Therapy for MS: Important Considerations

The availability of an oral agent for MS may create a therapeutic dilemma for clinicians as they try to determine the role of new therapy in patient care.

By Jeffrey I. Greenstein, MD

The introduction of any new disease-modifying agent for Multiple Sclerosis (MS) is a welcome event, especially if this is an oral medication. An addition to our armamentarium of MS therapies is likely to be particularly valuable if the agent has a different mechanism of action than therapies currently available (especially when sub-optimal responses occur); and particularly if given orally, as this is likely to receive greater patient acceptance, convenience and compliance. The approval of fingolimod/FTY720 (Gilenya™, Novartis)[1] by the FDA last year was such an event. However, a careful evaluation of the treatment outcomes and safety data raises questions about the optimal use of the drug as a disease modifier in MS, as well as concern regarding the safety profile, particularly given a relatively limited experience with the drug and the potential for relatively rare but serious events both on the MS process as well as on other body systems.[2]

Fingolimod (FTY720, Gilenya™; 2-amino-2propane-1,3-diol hydrochloride), derived from Isaria sinclairii, a structural analog of sphingosine-1-phosphate (S1P) is a sphingosine-1-phosphate receptor modulator acting as an agonist/antagonist following receptor binding and then internalization.[3,4] It is phosphorylated by sphingosine kinase[5] to the biologically active form FTY720-P, which acts on four of the five G-protein coupled S1P-receptors (SIP-1, SIP-3, SIP-4 and SIP-5).[6] These receptors are widely distributed, and their pleiotropic activation affects a myriad of processes including central nervous system development,[7] regulation of lymphocyte egress from lymph nodes and thymus,[8-10] vascular endothelium,[11] cardiovascular system, and oligodendroglia and astrocytes in particular.[6] FTY720 crosses the blood-brain-barrier[12] and localizes particularly in myelin.[13] The effects of fingolimod on SP-receptors differs depending upon the cell and its state of activation or differentiation, on whether it acts as an agonist or antagonist, the concentration and duration of exposure, and vascular effects on organs and tissues. Additionally, the effect of fingolimod is potentially influenced by and influences the cytokine milieu. It is also difficult to extrapolate from potentially beneficial actions in vitro to possible effects in

vivo in humans. These factors may significantly influence outcome in therapy in MS as well as the development of adverse events.

Efficacy Data

FTY720 was demonstrated to be effective in experimental allergic encephalomyelitis (EAE) induced by both spinal cord and myelin antigens in a number of models.[13-17] Administration of FTY720 stabilized the blood-brain-barrier and reduced the expression of vascular adhesion and pro-inflammatory molecules resulting in both improved clinical and pathological (inflammatory, demyelinating and axonal sparing) features.[13-14] Examination of both active and chronic MS lesions demonstrated up-regulation of S1P1- and S1P3-receptor levels (which bind FTY720) by immunohistochemistry in both active and chronic MS lesions.[18] The study did not include examination of S1P5-receptors (also FTY720 targets) and thus, unfortunately, did not examine the predominant receptor type in oligodendroglia. The findings, most in acute EAE, provided the rationale for investigation of FTY720 in MS.

The initial phase II clinical study[19] randomized patients to fingolimod 5.0mg and 1.25mg doses compared with placebo for six months. The primary endpoint of total cumulative number of Gadolinium-enhancing (Gd) lesions was reached with a significant reduction in both doses compared with placebo (5.0mg: 5.7, 61 percent reduction; 1.25mg: 8.4, 43 percent reduction; placebo, 14.8). The annualized relapse rate was likewise significantly reduced (5.0mg: 0.36, 53 percent reduction; 1.25mg: 0.35, 55 percent reduction; placebo: 0.77). The secondary measures were significantly reduced except for EDSS score change, which is not unexpected in a short duration study.

Two phase III trials were then begun; the first a 24-month, double-blind, randomized trial evaluating fingolimod 1.2mg and 0.5mg daily against placebo (FREEDOMS)[20] and the second comparing fingolimod at the same daily doses with Avonex™ in a 12-month, double-blind, double-dummy study (TRANSFORMS).[21] In the FREEDOMS study there was a statistically significant reduction in relapse rate (based on a negative binomial regression model adjusting for study group, country, number of relapses within two years prior to baseline and baseline EDSS) between the fingolimod doses and placebo (0.5mg: RR 0.18, 55 percent reduction; 1.25mg: RR 0.16, 60 percent reduction; placebo: 0.40). The unadjusted rates differed somewhat, although they remained significantly different for both fingolimod doses (0.5mg: RR 0.21, 55 percent reduction; 1.25mg: RR 0.19, 55 percent reduction; placebo: 0.47).[2] The cumulative probability of disease progression based on three-month confirmed EDSS progression was 17.7 percent for 0.5mg and 16.6 percent for 1.25mg, versus placebo 24.1 percent. This represents a 27 percent reduction in disability for the 0.5mg dose and a 31 percent reduction for the 1.25mg dose. Numerous MRI parameters were studied and found to be statistically significant—the Gd-enhanced data serves as an example of the results where there was an 82 percent reduction in Gd-enhancing lesions at 24 months in both fingolimod groups compared with placebo. Additionally, the brain atrophy data for the 24-month point (measured as loss of brain volume) was -0.89 for the 1.25mg dose (32 percent decrease) and -0.84 for the 0.5mg dose (36 percent decrease), versus -1.31 for placebo.

The Fingolimod/Avonex comparison study (TRANSFORMS)[21] demonstrated a significant reduction in relapses and Gd-lesions in both fingolimod groups (1.25mg: RR 0.20, 39 percent reduction; 0.5mg: RR 0.16, 51 percent reduction; Avonex, RR 0.33 – and Gd: 1.25mg, 0.14, 72% reduction, 0.5mg, 0.23, 55% reduction; Avonex 0.51). In contrast, there was not a significant difference in progression of disability between the groups,[2,21] and the changes in brain volume were modest though statistically significant (1.25mg: -0.30 percent, 33 percent reduction; 0.5mg: -0.31 percent, 31 percent reduction; Avonex: 0.45 percent).

There has been a consistent gradient of effects in trials of drugs in MS with reduction of Gd-lesions > relapse rate > reduction in brain volume > disability progression. What is surprising in the case of fingolimod is the robust effect on relapse rate and enhancing lesions compared with a more modest effect on brain atrophy and disability; particularly

because the clinical disability of fingolimod-treated patients did not significantly differ from Avonex-treated subjects in the TRANSFORMS study. Many reasons could explain these differences, but definitive data to explain this dissociation of outcomes is lacking. This differential effect could potentially occur if there was a loss of efficacy of fingolimod in the brain relative to its beneficial effects in reducing peripheral lymphocytes (which is thought to be the operative mechanism in MS). In this scenario, fingolimod would be effective in preventing penetration of the CNS by pathogenic mononuclear cells and demyelination, analogous to the case in EAE. However, the benefits would be counterbalanced by fingolimod's pleiotropic actions resulting in deleterious effects such as ineffective modulation of mononuclear cells already *in situ* or potentiation of demyelination or inhibition of re-myelination. Potential contributing factors include a change in endothelial permeability of cerebral vessels,[44-47] either lack of effect on or activation of pro-inflammatory responses in mononuclear cells,[48] and potential cerebral toxicity (such as induction of apoptosis,[22,23] axonal injury, enhanced astrocytosis[49,50] or modulation of re-myelination and repair[24,50-53]). These factors alone or in combination might result in increased brain water which would produce a false positive result in measuring reduction of brain atrophy.[25-28]

Patient Montoring and Adverse Events

In addition to the treatment outcomes, the adverse event profile of fingolimod is also a cause for concern because of the range of complications and the cumulative occurrence of complications. It is theoretically possible that had doses lower than 0.5mg been evaluated clinical efficacy might have been retained with fewer adverse events. The dose responses in the data in both the MS[19-21] and renal transplant studies[29-31] would support this possibility. The relatively high drop-out rates in the trials partly reflects the occurrence of these adverse events.

Nine deaths occurred in the MS treatment protocols.[2] These included fatal HSV1 and VZV infections, lymphoma, metastatic tumor, and what appears to be a rapid acceleration of MS or similar demyelinating condition. The 0.5mg dose appeared to be safer than the higher doses. However, the study subjects were in general good health so that the more widespread use of fingolimod in the presence of concurrent conditions (e.g. hypertension, diabetes, coronary artery disease and ocular disease) might potentially increase risk. In addition, the relatively small number of patients studied and the comparatively short duration of exposure might not reveal potential risks, such as the occurrence of rare events that are more likely to manifest with a larger and longer exposure to the drug. The increased occurrence of herpetic infections (deaths and less serious infections), lymphoma, and skin malignancies is consistent with a state of immunosuppression.[31-34] The primary immunological mode of action of FTY720 is believed to be the retention of lymphocytes in lymph nodes without immunosuppression; but these clinical features are more consistent with the presence of either qualitative or quantitative immunological defects, and despite the absence of the whole range of other opportunistic infections, they are similar to complications seen with the use of other immunosuppressive agents.

Despite the data from T-cell phenotyping in fingolimod exposure,[35,36] which suggests the retention of protective immunity, we have very little actual information on the effect of FTY720 on immune function in humans and we particularly lack data on antigen specific immune responses.[37,38] The surface phenotypes of human T-cells are not immutable and unlike T-cells in the mouse, human T-cells can change phenotype and function depending on the specific cytokine milieu—so that one cannot place too much reliance on surface markers alone in the absence of functional immune data.[39] It is therefore possible that subtle immune defects exist with FTY720 treatment which might allow the complications of immunosuppression. That said, it is also intriguing that there were instances of worsening of MS in the face of FTY720 therapy. Autoimmunity can occur alongside immunosuppression, and the factors above might underlie this occurrence. In addition, diverse immunologic changes result from FTY720 exposure, and these could be operative. For example, FTY720 can reduce T-regulatory cell function,[38,40] stimulate the

production of pro-inflammatory cytokines,[41-43] and potentially breach the blood-brain-barrier[44-46] (possibly by increased VCAM-1 and E-selectin[47] expression), which might allow the entry of pathogenic mononuclear cells into the brain producing more aggressive demyelination.

Other adverse events which can be explained from knowledge of the effects of both FTY720 and S-1P are considered by the affected system.

Cardiac. With the initiation of therapy, bradycardia and first and second degree heart block were noted in some subjects. Elevation of both systolic and diastolic blood pressure above baseline as well as the occurrence of overt hypertension were also noted.[2,19-21] These occurrences were most likely related to the known effects of S1P on heart rate,[54] vascular tone,[55] vascular permeability,[56] and angiogenesis.[6] Toxicity studies of FTY720 in animals also revealed cardiac papillary vascular wall thickening and perivascular and focal perimysial fibrosis.[2] Because of these findings, patients initiating therapy require observation for at least six hours as well as access to cardiac care if needed. Given that even mild blood pressure elevation increases cardiovascular risk in the long term, it is probably wiser to discontinue the medication if elevated blood pressure persists—at least until a larger data set is available for review. A similar vascular effect on the kidney might occur, but data are insufficient to draw conclusions in the MS population. The use of fingolimod in MS patients at increased risk for vascular and renal disease has not been established because the MS study populations were healthy. Given this, it is probably wiser to use fingolimod therapy cautiously in individuals at risk for cardiovascular and renal disease.

Pulmonary. There was a slight increase in dyspnea and wheezing in small numbers of fingolimod-treated individuals. Pulmonary function abnormalities (PFT) were noted in FEV_1, FVC, and DLCO in some individuals, but these were not consistently related to clinical symptoms. The trend overall was for an ongoing decrease in these PFT parameters in treated subjects, which proceeded at a greater rate than that of the control subjects.[2] In symptomatic individuals it is helpful to evaluate a high resolution chest CT. The basis for these findings is not yet explained but may possibly relate to FTY720-induced changes in regulation of vascular tone and endothelial permeability,[2] as well as possible bronchoconstriction and decreased diffusion capacity of the lung.[2] Toxicity studies in animals did reveal foci of inflammation, pulmonary congestion, bronchiolar smooth muscle hypertrophy, collagen deposition in alveolar ducts and bronchioles, and subpleural fibrosis[2] in the lung, and these factors might also contribute to the decline in pulmonary function. Early studies demonstrated that FTY720 enhanced lung permeability barriers in short-term studies.[57] However, the chronic administration of FTY720 might produce a different result, with the exacerbation of pulmonary vascular leak particularly with additional provocative stimuli.[44]

Central Nervous System. A small number of seizures occurred in the fingolimod-treated subjects and more frequently in the 1.25mg treated individuals.[2] MS patients have an increased risk of seizures, and this risk might be heightened by fingolimod treatment. Seizures also occurred more frequently in the renal transplantion experience, albeit at the use of higher drug doses and in the setting of other conditions.[2] Sphingosine-1-phosphate and the S-1-P receptor

Table 1. Recommended Baseline Screening and Ongoing Safety Monitoring Parameters

Check HZV serology
CBC, Differential, Platelets
Electrolytes
LFT
Screen cardiac and respiratory status
EKG
Monitor cardiac function with initiation of therapy
PFT, DLCO
High resolution chest CT, if indicated
Opthalmology Evaluation
Visual Fields
Optical Coherence Tomography
Dermatology Evaluation

may differentially modulate neurons. In the absence of the receptor, there is pyramidal cell hyper-excitability with seizures.[58] In contrast, S-1-P can enhance sensory neuron excitability.[59] These mechanisms might thus underlie the occurrence of seizures.

A case of posterior reversible leukoencephalopathy was seen in the 5mg group only.[19] Whether this is indicative of a fingolimod dose effect, or similar to the sporadic occurrence of this syndrome seen with other drugs is not clear.

Cerebral blood flow (CBF) was normal in short-term studies of FTY720, but the chronic administration of fingolimod on CBF has not been evaluated.[2] One case of stroke and two cases of peripheral vascular disease were noted in 1.25mg fingolimod-treated subjects.[2] In addition, a case of hemorrhagic encephalitis occurred at the 1.25mg dose.[59] S-1P, the S-1P3 receptor and phospho-FTY720 all induce cerebral vasoconstriction, and this effect is potentiated by TNF-α. These alone or in combination may play a role in the pathogenesis of stroke in this setting.[60,61] The inflammation here may have the same basis as discussed above.

Ocular Disorders. Macular edema presented as decreased or blurred vision, a sense of ocular pressure and decreased visual acuity, and this was confirmed with OCT and fluorescein angiography.[2] Most cases resolved after discontinuation of drug. Retinal hemorrhages and aneurysms were seen in the 1.25mg group only. A small number of cases of bilateral retinal ischemia, retinal microthrombosis, retinal hemorrhage and aneurysms also occurred, probably reflecting the vascular effects of the drug as well.

Laboratory and Other Abnormalities. Lymphopenia occurred to a level of approximately 30 percent of normal as expected from the known redistribution of these cells to lymph nodes by FTY720. With cessation of therapy, lymphopenia resolves in about three months, probably in part due to the long half-life of the drug.[2] Increased LFT were relatively frequent and a common cause of drug discontinuation.[2] Because of this, the use of concomitant drugs with hepatotoxic effects should be carefully monitored as these may further increase risk.

Autoimmunity. The cases of apparent acceleration of MS as well as idiopathic autoimmune thrombocytopenia raise concerns that accentuation or induction of autoimmunity might occur in a small number of individuals treated with fingolimod. While it is difficult to extrapolate from the renal transplant experience to MS—because of the concomitant use of other immunosuppresants with FTY720 and because of the presence of other conditions—it is notable that there was an excess of both humoral and cell-mediated immune rejections noted in the fingolimod-treated transplant subjects.[29,30]

Neoplasms. The renal transplant experience with fingolimod included the occurrence of squamous cell carcinoma, Kaposi sarcoma, and lymphoma. Again, comparison with the MS population is difficult because they were healthier and received lower drug doses. This background, however, would support careful monitoring of MS patients until a larger cohort has been treated for longer durations of time.

Expanded Options

The introduction of fingolimod has expanded the therapeutic options available to treat MS. While quite effective in decreasing relapse rate (which potentially helps reduce long-term worsening by reduction of inflammation) its impact on disease progression due to the combined effects of inflammation and neurodegeneration has limitations. The adverse event profile is also broad, requiring careful baseline assessment and ongoing monitoring. In comparison with the currently available therapies, I believe fingolimod is probably best used in cases of relapsing-remitting MS refractory to other treatments rather than as an initial therapy. ■

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1. Gilenya™ (fingolimod) capsules 0.5mg. wwwPDR.net

2. Food and Drug Administration (FDA). Peripheral and Central Nervous System Drugs. Advisory Committee Meeting. Fingolimod (NDA 22-527) Background Package. June 10, 2010.

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