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Is fingolimod an advancement in the treatment of multiple sclerosis?

Evaluation of: KAPPOS L, ANTEL J, COMI G. *et al.*: Oral fingolimod (FTY720) for relapsing multiple sclerosis. *N. Engl. J. Med.* (2006) **355**:1124-1140.

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Fingolimod is an agonist at sphringosine-1 phosphate receptors that reduces circulating T lymphocytes. Experimental autoimmune encephalomyelitis is often used as an animal model of multiple sclerosis (MS), and fingolimod prevents or reverses this encephalomyelitis. In subjects with relapsing MS, fingolimod reduced the total number of gadolinium-enhanced lesions detected by MRI, and the total volume of these lesions at 6 months. The annualised relapse rate was 0.77 in the placebo group, and was lowered to 0.35 and 0.36 in the 1.25- and 5.0-mg fingolimod groups, respectively. However, there was no difference in Expanded Disability Status Scale score between untreated MS patients and those treated with fingolimod. After the 6-month core study, all subjects were treated with fingolimod. The annualised relapse rate remained low and the Expanded Disability Status Scale score remained steady for up to 24 months. Fingolimod decreased heart rate and blood pressure. Given the modest clinical benefits reported to date with fingolimod, long-term safety studies need to be undertaken with fingolimod to determine whether the benefit/risk profile justifies the routine use of fingolimod in subjects with relapsing MS.

Keywords: encephalomyelitis, fingolimod, relapsing multiple sclerosis

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1. Introduction

Multiple sclerosis (MS) is an autoimmune, inflammatory, demyelinating disease of the CNS. Patients with MS commonly present with an individual mix of neuropsychological dysfunction, which tends to progress over years to decades. In the US, the incidence of MS is 0.5 – 1.0 per 1000 people. Approximately 70% of patients suffer from relapsing-remitting MS, which is characterized by acute exacerbations with full or partial remissions. Subjects with relapsing-remitting MS are treated with methylprednisolone during exacerbations, and with β-IFNs or glatiramer acetate (a synthetic form of myelin basic protein) to reduce relapses [101]. Despite treatment with β-IFN or glatiramer, many MS patients still have relapses.

In MS, $CD4^+$ T cells destroy oligodendrocytes, which synthesise and maintain axonal myelin sheathes in the CNS. In autoimmune diseases such as MS, subjects harbour, rather than eliminate T cells that can become activated by self-antigens. A recent immunotherapeutic approach to treating MS is natalizumab – a monoclonal antibody that blocks the adhesion of the α_4 integrin-dependent adhesion of blood-borne encephalitogenic T cells and macrophages to microvessels in the CNS (reviewed in [1]). Natalizumab has been trialled in MS and shown to decrease the lesions, but *JC polyomavirus*, a progressive, multifocal leukoencephalopathy has developed in three subjects [2].

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Another new immunotherapeutic approach to MS is fingolimod. Fingolimod (FTY720, 2-amino-2-(2-[4-octyl-phenyl]ethyl)-1,3-propanediol hydrochloride) is a chemical derivation of myriocin, a metabolite of the fungus *Isaria sinclairii*, used in Chinese traditional medicine [1,3]. In the bloodstream, fingolimod is phosphorylated and resembles lysophospholipid sphingosine-1 phosphate (S1P) [1,3]. S1P has at least five receptors and has roles in neurogenesis, cardiovascular development, vasoregulation, endothelial-cell function and leukocyte migration [1,3]. $S1P_1$ is expressed on lymphocytes and regulates lymphocyte migration. Fingolimod probably acts as an agonist at the $S1P_1$ receptors, and this subsequently leads to an internalization of the receptors and reduced lymphocyte migration [1]. It is proposed that in MS, fingolimod traps newly generated encephalitogenic T cells in the lymph nodes, and hence prevents them from migrating to the CNS [1].

Fingolimod was first shown to reduce circulating T lymphocyte levels in rats [3]. Acute experimental autoimmune encephalomyelitis (EAE) is an inflammatory disease of the CNS, which is often used as a model of MS. In the EAE model, where rats were immunised with an emulsion of bovine spinal cord, fingolimod (started at the same time as the immunisation) prevented the development of the disease [3]. In another rat model, in which EAE was induced with guinea-pig myelin basic protein, fingolimod (started at the same time as the immunization) completely protected against the disease [4]. The control EAE rats had inflammatory lesions in the CNS, which the fingolimod-treated rats did not have [4]. This protection was associated with reduced lymphocytes stained for T-cell receptors in the spinal cord [4]. When spleen cells from the control EAE rats were transferred to naive recipient rats, they developed EAE, whereas the transfer of spleen cells from fingolimod-treated EAE rats to naive recipients did not transfer the EAE [4].

More importantly, fingolimod has been shown to be effective after the EAE has been established in the relapsing-remitting EAE model in SJL mice [5]. In this model, the EAE is a chronic disease with a relapsing-remitting pattern [5]. In established EAE, fingolimod caused a peripheral lymphopenia, and a reversal of changes in expression of mRNAs encoding some myelin proteins and inflammatory markers [5]. Fingolimod also caused a rapid and sustained improvement in clinical status [5].

Recently, a clinical trial of fingolimod in relapsing MS has been undertaken, and shown promising results. This trial is the subject of this evaluation [6].

2. Methods and results

The methods and results of the Phase II proof-of-concept trial, showing that fingolimod reduced lesions in relapsing MS [6], are discussed in this section.

2.1 Methods

The study enroled subjects in 10 European countries, and Canada with relapsing MS and one of the following:

- Two or more relapses during the previous 2 years
- One or more relapses in the previous 1 year
- One or more gadolinium-enhanced lesions detected by MRI

Gadolinium-enhanced lesions are markers of the active nature of MS, regardless of clinical symptoms. Enroled subjects also had to have a score of 0 – 6 on the Expanded Disability Status Scale (EDSS), in which 10 is the highest disability, and have been neurologically stable for 30 days.

Subjects were excluded if they had recently taken corticosteroids, immunomodulatory therapy or immuno-suppressive treatment. Subjects were also excluded if they had low white cell or lymphocyte counts. The 277 enroled subjects had a mean age of ~ 38 years and were predominantly female (~ 70%), with a mean EDSS score of 2.6. Most of the subjects had suffered from MS for ~ 9 years, and were having a mean of 1 – 2 relapses/year.

In the first 6 months (core study), subjects received either placebo, or fingolimod 1.25 or 5.0 mg. Fingolimod is administered orally. In the 6-month extension study, subkects taking fingolimod continued to take it, and those taking placebo were randomised to fingolimod 1.25 or 5.0 mg.

2.2 Results from core study

The primary efficacy end point was the total number of gadolinium-enhanced lesions per patient recorded on T_1-weighted MRI, at monthly intervals for 6 months. In the placebo group this was a mean of 14.8, but this was reduced to 8.4 and 5.7 with fingolimod 1.25 and 5.0 mg, respectively.

Secondary MRI end points included the total volume of gadolinium-enhanced lesions per patient and this was 1418 mm^3 in the placebo group, and 715 and 530 mm^3 with fingolimod 1.25 and 5.0 mg, respectively. The proportion of patients with gadolinium-enhanced lesions was ~ 50% at baseline, and after 6 months this had increased to 62% in the placebo group, but decreased to 36 and 37% with fingolimod 1.25 and 5.0 mg, respectively. The total number of new lesions per patient on T_2-weighted images, over the 6 months, was 6.4 in the placebo group, but only 3.0 and 1.9 with fingolimod 1.25 and 5.0 mg, respectively. The change in lesion volume on T_2-weighted images was an increase of 129 mm^3, whereas there was a decrease of 113 and 627 mm^3 with fingolimod 1.25 and 5.0 mg, respectively.

Relapse was defined as the occurrence of new symptoms or worsening of previously stable or improving symptoms, lasting > 24 h, and accompanied by an increase of 0.5 in the EDSS score, or 1 point in the functional systems. Clinical end points included the number of patients remaining free of relapse at 6 months, which was 66% in the placebo and 86% with both fingolimod 1.25 and 5.0 mg. The annualised relapse rate was 0.77 in the placebo group, and this was lowered to 0.35 and 0.36 in the fingolimod 1.25- and 5.0-mg groups, respectively. There

was no difference in EDSS scores between untreated MS, subjects and those treated with fingolimod.

The first dose of fingolimod caused a decrease in heart rate of 13.8 and 16.6 bpm in the 1.25- and 5.0-mg groups, respectively. This effect decreased with subsequent doses. Mean blood pressure was initially decreased by 5 – 6 mmHg with fingolimod, but increased by 4 – 6 mmHg after 2 months of treatment. Pulmonary function tests showed a reduction in forced expiratory volume at 1 s (FEV_1) of 1.9, 2.8 and 8.8% in the placebo, fingolimod 1.5- and 5.0-mg groups, respectively.

Both doses of fingolimod caused increases in concentration of alanine aminotransferase in 10 and 12% of subjects (with 1.25 and 5.0 mg, respectively), compared with 1% of subjects in the placebo group. This effect of fingolimod decreased with continuing treatment, and reversed when fingolimod was stopped. Fingolimod caused a 20 – 30% reduction in peripheral-blood lymphocyte counts. No serious infections were reported.

Fingolimod 5.0 mg, but not 1.5 mg, increased the incidence of nasopharyngitis (placebo, 15%; fingolimod 5.0 mg, 28%), dyspnea (13 versus 1%), diarrhea (12 versus 2%), nausea (11 versus 2%). One patient, given fingolimod 5.0 mg for 10 weeks, developed posterior encephalopathy syndrome, which did not resolve completely when fingolimod was stopped. The subject was left with a right homonymous hemianopia (loss of half vision), associated with left occipital hyperintensity, and mild ataxia (loss of coordination) remaining at 15 months.

2.3 Results from extension study

Of the 277 subjects who completed the core study, 250 continued to the extension study, and continuing benefits were observed with fingolimod. Thus, the number of gadolinium-enhanced lesions remained low in those treated with fingolimod, while falling in those previously treated with placebo for 6 months and then fingolimod for 6 months. The proportion of patients with gadolinium-enhanced lesions continued to fall to 15% and 12% of subjects at 12 months, with fingolimod 1.25 and 5.0 mg, respectively. EDSS scores did not change over the 12 months.

The overall incidence of adverse effects was lower in the extension study. However, one subject, who changed from placebo to fingolimod 5.0 mg, developed facial herpes zoster, and another, who changed from placebo to fingolimod 1.5 mg, developed enterocolitis.

2.4 Results to 24 months

The subjects in the fingolimod trial have been followed for a further 12 months, and a summary of the results have been presented [102]. After 24 months, the number of subjects with gadolinium-enhanced lesions remained low at 9 – 21% [102]. The annualised relapse rate (0 – 24 months) remained low in all groups at 0.29 – 0.38 [102]. The EDSS values remained stable in all groups. The side effects of nasopharyngitis, headache and influenza remained higher with fingolimod 5.0 mg [102]. The open-label extension is to continue, with all subjects receiving fingolimod 0.15 mg [102].

3. Discussion

Given that two patients developed serious infections and one developed posterior reversible encephalopathy while taking fingolimod, larger studies need to be undertaken to assess the safety of fingolimod [6]. In addition, as fingolimod increased the concentration of alanine aminotransferase in some subjects, further studies are needed to evaluate any potential liver toxicity [6].

The authors conclude that oral fingolimod may be a treatment option for relapsing MS, but before this can be considered for general clinical use, large-scale trials of efficacy and safety are needed [6].

4. Expert opinion

4.1 Clinical outcome

Although there is no clearcut link between gadolinium-enhanced lesions and the signs and symptoms of MS, several agents that reduce gadolinium-enhanced lesions in MS have also been shown to reduce or prevent the decline in EDSS (e.g., IFN-β_{1a} [7], glatiramer acetate [8], natalizumab [9]). Over 6 months, fingolimod reduced gadolinium-enhanced lesions, but there was no difference in EDSS score between untreated MS subjects and those treated with fingolimod. It will be of interest as to whether there are any long-term improvements, or prevention of decline, of the clinical symptoms of MS with prolonged treatment with fingolimod. Unfortunately, this could not be determined from the extension study, as all subjects were given fingolimod.

4.2 Selective $S1P_1$ agonist

It has been suggested that the beneficial effects of fingolimod in MS are due to interaction with the $S1P_1$, whereas interaction with the other S1Ps may underlie the side effects of reduced heart rate, increased mean arterial blood pressure and airway obstruction [1]. Thus, the ability of fingolimod to decrease heart rate is probably due to stimulating the $S1P_3$/G protein-gated potassium channel, IK_{ACh} [10]. To overcome these side effects, it will be necessary to develop drugs that are selective for $S1P_1$, and this is already starting to happen. KRP-203 is a selective $S1P_1$ agonist being developed for use as an immunosuppressant in transplants [11], which did not induce bradycardia in the guinea-pig [12].

4.3 Ongoing trials with fingolimod in multiple sclerosis

Fingolimod is now in two large Phase III trials, one comparing the 1.25-mg dose with placebo, and the other comparing fingolimod with interferon in subjects with MS [102]. A lower dose of fingolimod is also to be evaluated [102].

4.4 Safety of fingolimod

Fingolimod is also being clinically developed as an immunosuppressant for long-term use in transplantation [13,14]. The safety data from the development of fingolimod for use in the treatment of MS and also in transplantation, may be able to be combined to determine the safety of fingolimod in large numbers of patients.

4.5 Is fingolimod an advancement in the treatment of multiple sclerosis?

Given the modest clinical benefits reported so far with fingolimod, long-term safety studies need to be undertaken with fingolimod to determine whether the benefit/risk profile justifies the routine use of fingolimod in subjects with relapsing MS.

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