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Oral Disease-Modifying Therapies for Multiple Sclerosis: Are We There Yet?

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Introduction

Current US Food and Drug Administration (FDA)-approved disease-modifying therapies (DMTs) for multiple sclerosis (MS) require either self-injection (the interferon- β products and glatiramer acetate) or intravenous infusion (natalizumab and mitoxantrone). MS patients and their physicians have long wanted an effective oral DMT. That wait soon may be over. Earlier this year, the results of phase 3 clinical trials of two oral immunosuppressants for MS, fingolimod (AKA FTY720) and cladribine, were published, and both agents were found to be effective [1-3]. FDA approval of these oral agents for the treatment of MS will be a historic landmark in MS therapeutics. This review focuses on fingolimod.

Fingolimod has a novel mechanism of action. It is a sphingosine 1-phosphate receptor modulator and inhibits lymphocyte egress from lymph nodes [4]. Previously, fingolimod showed beneficial effects on clinical and MRI parameters in a 3-year phase 2 study involving patients with relapsing MS [5].

This report reviews the results from the two phase 3 clinical trials of fingolimod in MS, one comparing two different doses of fingolimod with placebo [1] and the other comparing two different doses of fingolimod with interferon- β -1a [2]. First we discuss the results of the double-blind, placebo-controlled phase 3 trial of fingolimod called FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis) that compared two different doses of fingolimod with placebo [1]. We then discuss the 12-month double-blind, double-dummy study called TRANSFORMS (Trial Assessing Injectable Interferon Versus FTY720 Oral in Relapsing–Remitting Multiple Sclerosis) [2].

Aims

The FREEDOMS trial studied the efficacy and safety of oral fingolimod at a dosage of 0.5 or 1.25 mg/d or placebo treatment for 24 months in patients with relapsing–remitting MS (RRMS). The primary outcome was the annualized relapse rate (ARR). The significant secondary outcomes included time to confirmed disability progression (defined as a one-point increase in Expanded Disability Status Score [EDSS]) and MRI brain measures including number of gadolinium-enhancing lesions, changes in number and volume of T2-weighted

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lesions, and change in brain volume between baseline and 24 months. The safety of the two fingolimod doses was compared with that of placebo.

The TRANSFORMS trial compared the efficacy and safety of two different oral fingolimod doses, 1.25 and 0.5 mg, with those of intramuscular interferon- β -1a (Avonex; Biogen Idec, Cambridge, MA) over a 12-month period. The primary end point of this study was the annualized relapse rate. Major secondary end points included brain MRI parameters such as the number of new or enlarged lesions on T2-weighted scans at 12 months and disability progression sustained for at least 3 months.

Methods

The FREEDOMS trial assigned 1,272 MS subjects to receive one of the two doses of oral fingolimod or placebo, in a 1:1:1 randomization. Subjects were included if they were 18 to 55 years old, met the revised McDonald criteria for MS, and had a relapsing–remitting course. They also were required to have had one or more documented relapses in the previous year, or two or more in the previous 2 years, and an EDSS of 0 to 5.5. Subjects had to be free of active infection, a clinically significant systemic disease, and immune suppression, among other exclusionary criteria.

The TRANSFORMS study randomly assigned 1,292 patients with RRMS to receive daily oral fingolimod at a dose of either 1.25 or 0.5 mg or a weekly intramuscular interferon- β -1a dose of 30 μ g. Subjects receiving fingolimod also took a weekly intramuscular placebo, and those receiving interferon- β -1a took a daily oral placebo. Inclusion and exclusion criteria were the same as those of the FREEDOMS trial.

Results

Of 1,272 subjects randomized in the FREEDOMS trial, 1,033 (81.2%) completed the study. There was a significant improvement in the ARR, the primary outcome, in the fingolimod-treated subjects compared with the placebo group (ARR, 0.18 in the 0.5-mg group, 0.16 in the 1.25-mg group, and 0.40 in the placebo group; $P<0.001$ for either dose vs placebo). Both fingolimod doses also showed a significant effect on risk reduction of disability progression over the 24-month period (hazard ratio, 0.70 and 0.68, respectively; $P=0.02$ vs placebo, for both comparisons). During this period, the placebo group (24.1%) had worsened disability (confirmed worsening in EDSS after 3 months) compared with both fingolimod groups (16.6% in the 1.25-mg group, $P=0.01$, and 17.7% in the 0.5-mg group, $P=0.03$). Fingolimod-treated subjects showed significantly improved MRI-related measures (number of new or enlarged lesions on T2-weighted images, gadolinium-enhancing lesions, and brain volume loss; $P<0.001$ for all comparisons at 24 months) compared with the placebo-treated subjects.

Of 1,292 patients randomized in the TRANSFORMS trial, 1,153 (89%) completed the study. The ARR was significantly improved in both fingolimod groups (ARR, 0.20 in the 1.25-mg group and 0.16 in the 0.5-mg group vs 0.33 in the interferon group; $P<0.001$ for both comparisons). Both fingolimod-treated groups showed significant improvement in most brain MRI outcome measures, except for the change in lesion volume, compared with the interferon-treated group. Overall disability progression was not common in any of the three study groups. All the intervention groups were comparable in disability progression, as determined by EDSS change; worsening occurred in 6.7% of patients in the interferon- β -1a group, 7.9% in the 1.25-mg fingolimod group, and 5.9% in the 0.5-mg fingolimod group.

The common adverse events in both phase 3 fingolimod studies were bradycardia, atrioventricular conduction block, macular edema, elevated liver enzyme levels, and mild hypertension. There was one case of skin cancer and 10 cases of nonfatal herpesvirus infection

in the fingolimod group (vs four cases of nonfatal herpesvirus in the placebo group) in the FREEDOMS trial. Among patients receiving the 1.25-mg dose in the TRANSFORMS trial, there were two cases of fatal infection, one of disseminated primary herpes varicella zoster and the other of herpes simplex encephalitis. Two additional deaths were reported in patients receiving the same fingolimod dose after the study ended. One subject had continued neurologic deterioration despite discontinuing the study drug at 11 months, and another subject died of metastatic breast cancer 10 months after discontinuing fingolimod.

Discussion

Compared with both placebo and interferon- β -1a, both doses of oral fingolimod improved the ARR and brain MRI outcomes, and over 2 years fingolimod reduced the risk of worsening disability compared with placebo. These benefits will need to be weighed against possible long-term risks.

Comments

The potential availability of an effective oral therapy for MS is exciting, particularly because fingolimod was superior in efficacy not only to placebo but also to interferon- β -1a. The promising advantages of fingolimod include the absence of injection site reactions and potentially better efficacy than that of currently available first-line agents. However, fingolimod sequesters lymphocytes in the lymph nodes and must be considered an immunosuppressant. The occurrence of two fatal herpes infections in the TRANSFORMS trial and the suggestion of an increased risk of cancer are of concern. We have more than 10 years of experience with the interferon- β products and glatiramer acetate, and this experience has established the long-term safety of these medications. Assuming the FDA approves fingolimod for MS, we believe this agent initially should be considered a second-line therapy for patients whose MS cannot be controlled with interferon- β or glatiramer acetate. We hope a robust safety monitoring program is established to enable us to determine the long-term safety of fingolimod.

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