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CLINICAL TRIAL

Fingolimod first-dose effects in patients with relapsing multiple sclerosis concomitantly receiving selective serotonin-reuptake inhibitors

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Abstract
Selective serotonin-reuptake inhibitors (SSRIs), commonly administered for depression and anxiety in patients with multiple sclerosis, are associated with QT interval prolongation. Fingolimod (FTY720; Gilenya®, Novartis Pharma AG) is a first-in-class sphingosine 1-phosphate receptor modulator approved for relapsing forms of multiple sclerosis. Fingolimod first-dose administration is associated with a transient, generally asymptomatic, slowing of heart rate, which may also prolong QT interval. This posthoc analysis compared cardiac outcomes in over 3300 patients with relapsing multiple sclerosis who were or were not receiving SSRIs during fingolimod treatment initiation, including a subset of patients receiving citalopram or escitalopram. Vital signs were recorded hourly for 6 h, and electrocardiograms were obtained pre-dose and 6 h post-dose. Changes in mean hourly heart rate from baseline (pre-dose) to 6 h post-dose were similar among patients not receiving SSRIs (fingolimod 0.5 mg, −7.5 bpm; placebo, 0.0 bpm) and those receiving SSRIs (fingolimod 0.5 mg, −6.6 bpm; placebo, 0.3 bpm). In patients treated with fingolimod 0.5 mg, the mean change in corrected QT interval from

Abbreviations: AV, atrioventricular; AVB, atrioventricular block; ECG, electrocardiogram; FDA, US Food and Drug Administration; FDO, first-dose observation; FREEDOMS, FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis; GIRK, G-protein-gated inwardly-rectifying potassium; HR, heart rate; MS, multiple sclerosis; QTc interval, QT interval corrected for heart rate; QTcB interval, QT interval corrected for heart rate using Bazett's correction method; QTcF interval, QT interval corrected for heart rate using Fridericia's correction method; S1PR, sphingosine 1-phosphate receptor; SSRI, selective serotonin-reuptake inhibitors; TRANSFORMS, Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis

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baseline to 6 h after treatment initiation was under 10 ms, and few patients had absolute corrected QT intervals of over 450 ms (men) or 470 ms (women), calculated according to Bazett's or Fridericia's correction methods, irrespective of whether or not they were receiving an SSRI; similar findings were reported in the placebo group. Co-administration of SSRIs and fingolimod was not associated with an increased incidence of any electrocardiogram findings compared with fingolimod therapy alone, and the majority of patients receiving fingolimod (83-86%) were discharged from first-dose monitoring at 6 h irrespective of whether they were also receiving SSRIs. These analyses provide reassurance that concomitant use of SSRIs does not affect cardiac outcomes associated with fingolimod treatment initiation.

1. Introduction

Depression and anxiety are common in patients with multiple sclerosis (MS), with prevalences higher than those observed both in the general population and in patients with other chronic diseases (Patten et al., 2003). The annual prevalence of depression in patients with MS is estimated to be up to 14%, with a lifetime prevalence of up to 50% (Goldman Consensus Group, 2005); anxiety disorders are estimated to affect more than 30% of patients with MS (Korostil and Feinstein, 2007).

Selective serotonin-reuptake inhibitors (SSRIs) are widely prescribed for the treatment of patients with depression and anxiety, including in those with MS (Koch et al., 2011). There is, however, some evidence that SSRIs are linked to QT interval prolongation (Funk and Bostwick, 2013). In particular, citalopram appears more likely to be associated with this effect than other SSRIs, and the US Food and Drug Administration (FDA) has issued revised recommendations for the use of the drug owing to a potential risk of abnormal heart rhythms when it is used at high doses (US Food and Drug Administration, 2012c).

Fingolimod (FTY720; Gilenya®, Novartis Pharma AG) is a first-in-class sphingosine 1-phosphate receptor (S1PR) modulator (Brinkmann et al., 2010; Chun and Hartung, 2010), approved for relapsing forms of MS as a once-daily oral therapy at a dose of 0.5 mg (European Medicines Agency, 2011; US Food and Drug Administration, 2012b). The efficacy benefits of fingolimod over both placebo and intramuscular interferon β-1a on key measures of disease activity (relapse rates, disability progression versus placebo, lesion load and brain volume loss) have been established in clinical trials (Calabresi et al., 2014; Cohen et al., 2010; Kappos et al., 2010). Fingolimod is associated with a transient, generally asymptomatic reduction in heart rate (HR) and, rarely, with generally asymptomatic atrioventricular (AV) block on treatment initiation, which are expected pharmacodynamic effects (Schmouder et al., 2006). Binding of fingolimod phosphate (the active phosphorylated compound) to S1PR subtype 1 on cardiac myocytes activates G-protein-gated inwardly-rectifying potassium (GIRK) channels (similar to the vagal stimulus), causing the transient reduction in HR. With continued administration of fingolimod, S1PRs are internalized and degraded, which leads to progressive resolution of the bradycardia over subsequent hours to days of treatment (Schmouder et al., 2006). In phase 3 clinical studies in patients with MS, the HR effect was maximal on day 1 and had recovered to baseline levels within 1 month of fingolimod initiation (DiMarco et al., 2015).

In a thorough QT interval study, fingolimod administered at 1.25 mg and 2.5 mg doses resulted in prolongation of the corrected QT interval (QTc), with the upper bound of the 90% confidence interval being an increase of 14.0 ms; although there was no consistent increase in the incidence of QTc interval outliers associated with fingolimod treatment (US Food and Drug Administration, 2012b). In the fingolimod clinical study program, clinically relevant prolongation of the QT interval was not observed at the approved fingolimod 0.5 mg dose (US Food and Drug Administration, 2012b). However, because of the effect of bradycardia on QT interval duration, the US fingolimod label guidelines currently recommend that patients receiving concurrent therapy with QT interval-prolonging drugs, with a known risk of causing torsades de pointes, should be observed overnight with continuous electrocardiogram (ECG) monitoring after their first dose of fingolimod (US Food and Drug Administration, 2012b). SSRIs are generally classified as QT interval-prolonging drugs, though only citalopram is listed by name in the fingolimod prescribing information as having a known risk of torsades de pointes (US Food and Drug Administration, 2012b). In the EU, the fingolimod Summary of Product Characteristics recommends that medicinal products that prolong the QTc interval are avoided in patients with relevant risk factors such as hypokalemia, hypomagnesemia or congenital long-QT interval syndrome (European Medicines Agency, 2011).

It is important to assess whether concomitant administration of fingolimod and SSRIs results in any unexpected first-dose effects in patients with MS. Here, we analyzed safety data from over 3300 patients with relapsing MS who were enrolled in the fingolimod clinical trial program to compare cardiac outcomes during treatment initiation in patients who were or were not receiving an SSRI, including a subset of patients receiving citalopram or escitalopram.

2. Methods

2.1. Study design and participants

These analyses included all patients randomized to receive fingolimod 0.5 mg, fingolimod 1.25 mg or placebo in the core, controlled parts of the phase 2 (ClinicalTrials.gov identifier NCT00333138) and the phase 3 FREEDOMS (NCT00289978), FREEDOMS II (NCT00355134) and TRANSFORMS (NCT00340834)