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First-dose effects of fingolimod: Pooled safety data from three phase 3 studies

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Abstract
Fingolimod treatment initiation is associated with a transient slowing of heart rate and atrioventricular conduction. This report presents first-dose fingolimod effects (0.5 mg or 1.25 mg) on cardiac parameters using phase 3 FREEDOMS, FREEDOMS II and TRANSFORMS pooled study data (n=3635 patients). Vital signs were recorded hourly for $\geq$6 h; 12-lead electrocardiogram (ECG) was obtained at baseline and at 6 h post-dose. Clinical events were graded at the first-dose administrator's discretion. At screening, on day 1 and at month 3, 1073 patients underwent 24-h ambulatory electrocardiogram monitoring. A transient decrease in mean measured heart rate occurred 4–5 h after the first dose, with a maximum reduction of 8 (fingolimod 0.5 mg) and 11 beats per minute (fingolimod 1.25 mg) below baseline. Symptomatic

Abbreviations: ACh, acetylcholine; AECG, ambulatory electrocardiogram; AV, atrioventricular; AVB, atrioventricular block; BP, blood pressure; bpm, beats per minute; ECG, electrocardiogram; fingolimod-P, fingolimod phosphate; FREEDOMS, FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis; $G_{\alpha i}$, inhibitory G protein; $G_{\beta\gamma}$, G-protein subunits; GIRK, G-protein-gated, inward rectifying potassium; HR, heart rate; IFN, interferon; IM, intramuscular; K^+, potassium ion; M2, muscarinic acetylcholine receptor M2; MS, multiple sclerosis; QTcI, corrected QT interval; $S1P_1$, sphingosine 1-phosphate receptor subtype 1; S1PR, sphingosine 1-phosphate receptor; SD, standard deviation; SVT, supraventricular tachycardia; TRANSFORMS, Trial Assessing Injectable Interferon Versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis; VPC, ventricular premature complex; VT, ventricular tachycardia

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bradycardia at treatment initiation was reported in 0.6% (fingolimod 0.5 mg) and 2.1% (fingolimod 1.25 mg) of patients; events were typically mild or moderate in severity, and most resolved spontaneously. Atrioventricular (AV) conduction delays were observed in a few patients (Wenckebach (Mobitz type I) second-degree AV block, fingolimod 0.5 mg, 0.2%; 1.25 mg, 1%: 2:1 AV block fingolimod, 0.5 mg, 0%; 1.25 mg, 0.2% on ECG 6-h post-dose). These were usually well tolerated and first occurred within 6 h of dosing. Consistent with its effects on atrial myocytes, fingolimod treatment initiation induced a transient slowing of heart rate and AV conduction. However, symptomatic bradycardia and second-degree AV block were uncommon and did not require intervention.

1. Introduction

Fingolimod (FTY720) 0.5 mg once daily (Gilenya®, Novartis Pharma AG, Basel, Switzerland) is a first-in-class sphingosine 1-phosphate receptor (S1PR) modulator (Brinkmann et al., 2010; Chun and Hartung, 2010) that has been approved in many countries as an oral therapy for relapsing forms of multiple sclerosis (MS) (European Medicines Agency, 2011; US Food and Drug Administration, 2010).

The clinical effects of fingolimod 0.5 mg and 1.25 mg in MS have been evaluated in a clinical program that included three phase 3, double-blind, randomized, controlled trials: FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis) (Kappos et al., 2010), FREEDOMS II (Calabresi et al., 2014) and TRANSFORMS (Trial Assessing Injectable Interferon Versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis) (Cohen et al., 2010). These studies showed that fingolimod had superior efficacy to both intramuscular (IM) interferon beta-1a and placebo, with benefits extending across clinical and magnetic resonance imaging measures.

At treatment initiation, fingolimod has a negative chronotropic effect on heart rate and atrioventricular (AV) conduction, which is mediated via binding of the active phosphorylated compound to S1PR subtype 1 ($S1P_1$) on atrial myocytes (Schmouder et al., 2006). Binding of fingolimod phosphate also induces internalization of the $S1P_1$ receptors. These internalized receptors are insensitive to stimulation by subsequent doses of the drug, thus limiting the negative chronotropic effects to the phase of treatment initiation.

This paper reports clinical cardiovascular experience and electrocardiogram (ECG) findings during fingolimod treatment initiation in the pooled population of 3635 patients from FREEDOMS, TRANSFORMS and FREEDOMS II, and 24-h ambulatory ECG (AECG) monitoring findings from 1073 patients from FREEDOMS II.

2. Methods

2.1. Study designs

The study designs, entry criteria and overall results for FREEDOMS (ClinicalTrials.gov identifier NCT00289978), FREEDOMS II (ClinicalTrials.gov identifier NCT00355134) and TRANSFORMS (ClinicalTrials.gov identifier NCT00340834) have been reported elsewhere (Calabresi et al., 2014; Cohen et al., 2010; Kappos et al., 2010).

In FREEDOMS ($n=1272$) and FREEDOMS II ($n=1083$), patients were randomly assigned to receive placebo or oral fingolimod 0.5 mg or 1.25 mg daily (see Fig. S1 for a patient flow diagram). In TRANSFORMS, 1292 patients were randomized to receive interferon beta-1a 30 μg (Avonex®, Biogen Idec, Weston, MA, USA) weekly by IM injection, or oral fingolimod 0.5 mg or 1.25 mg once daily.

2.2. Ethics statement

All studies adhered to the International Conference on Harmonisation Guidelines for Good Clinical Practice (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1996), and were conducted in accordance with the Declaration of Helsinki (World Medical Association, 2011). Study protocols were approved by the institutional review board at each study site. All patients provided written, informed consent before any study-related procedure was performed.

2.3. Exclusion criteria

Cardiovascular exclusion criteria relevant to this report included the following: recurrent syncope of suspected cardiac origin; myocardial infarction in the 6 months before study entry or current unstable angina; baseline resting heart rate less than 55 beats per minute (bpm); second-degree or higher AV block (AVB); sinus node dysfunction; congestive heart failure (Class III according to New York Heart Association Functional Classification); diabetes mellitus; coronary or peripheral arterial spasm; a corrected QT interval (QTcI) greater than 440 ms; concomitant use of Vaughan-Williams class 3 anti-arrhythmic drugs. Patients with controlled hypertension and those receiving therapy with either non-dihydropyridine-type calcium channel antagonists or β-blockers were not excluded.

2.4. Patient monitoring during first-dose administration

The initial dose of study treatment was administered by an independent physician acting as the first-dose administrator to preserve blinding. Patients were observed in a clinical