Multiple Sclerosis and Related Disorders (2014) 3, 408–412

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CASE REPORT

Abnormal rhythms in patients without known cardiac disease after a first dose of fingolimod

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Received 27 February 2013; received in revised form 26 October 2013; accepted 4 November 2013

KEYWORDS
Fingolimod;
Arrhythmia;
Relapsing-Remitting Multiple Sclerosis;
Atrio-ventricular block;
Accelerated idioventricular rhythm
Telemetry;
Telemetry

Abstract
Background: Fingolimod is used to reduce the rates of relapse and slow the progression of disability in relapsing-remitting multiple sclerosis (RRMS). In-office monitoring of patients for 6 h after the first dose of fingolimod is currently recommended due to rare cardiac rhythm disturbances. The objective of this paper is to describe our experience with continuous electrocardiographic monitoring of patients with RRMS starting on fingolimod.
Methods: Since changes to the FDA recommendations for first dose observation, a total of 59 patients with RRMS began treatment with fingolimod. After the first dose, all patients were observed for 6 h with continuous electrocardiographic telemetry, vital signs were checked every hour, and 12 lead ECG performed before and after the 6-h period.
Results: Three out of 59 (5%) patients developed arrhythmia that led to discontinuation of fingolimod. The first patient had a sinus bradycardia with idioventricular escape rhythm that lasted 45 s and two patients developed second-degree atrio-ventricular block Mobitz type I. None of the patients had a history of prior cardiacc disease or was taking other medications that may cause arrhythmia or bradycardia.
Conclusion: Continuous on-line electrocardiographic telemetry may detect abnormal rhythms in a small number of patients started on fingolimod. The clinical significance of these is unclear and warrants further study.

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1. Introduction

Fingolimod (FTY720, Gilenya®) is the first oral medication approved to reduce the rates of relapse and slow the progression of disability in relapsing-remitting multiple

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http://dx.doi.org/10.1016/j.msard.2013.11.001

sclerosis (RRMS) (Cohen et al., 2010; Kappos et al., 2010). Multiple sclerosis is an autoimmune disease that results in central nervous system demyelination. The exact mechanism remains unclear, but there is a strong evidence to support the role of T-cells in RRMS. Fingolimod acts as a sphingosine-1-phosphate (S1P) type 1 receptor antagonist. S1P receptors are found on T and B cells, in the heart, lungs and eyes. Fingolimod blocks the S1P receptor on T-cells in the lymph nodes and prevents their egress out of the lymph nodes (Graler and Goetzl, 2004).

The side effects of fingolimod on the cardiovascular system have been well described as bradycardia and atrioventricular blocks (AVB) (Cohen et al., 2010; Koyrakh et al., 2005; Kappos et al., 2010; Schmouder et al., 2012). In both phase III studies of fingolimod, a decrease in heart rate was noted after the first dose and peaked at 4–5 h after administration (Kappos et al., 2010; Cohen et al., 2010). Symptomatic bradycardia was reported in 0.7% of patients in the Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing–Remitting Multiple Sclerosis (TRANSFORMS study) (Cohen et al., 2010) and 2.1% in the FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS study) (Kappos et al., 2010). First-degree AV block was found in 0.2% and 0.5%, respectively. Second-degree AV block was reported in one patient in the TRANSFORMS study (0.2%) and none in the FREEDOMS trial (Cohen et al., 2010; Kappos et al., 2010). Reports of deaths in patients after the first dose of fingolimod have prompted health officials in the United States and Europe to launch safety investigations (Samson, 2012). No direct causality for sudden cardiac death has been established, but the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have revised prescription standards after the first dose of fingolimod (EMA, 2012; FDA, 2012). The new FDA safety communication was issued on May 15, 2012 (FDA, 2012). The FDA recommends that all patients starting fingolimod should be monitored for signs of bradycardia for at least 6 h after the first dose. Hourly pulse and blood pressure measurement and an electrocardiogram (ECG) prior to dosing and at the end of the observation period are recommended (FDA, 2012).

The FDA recommends that the duration of cardiovascular monitoring be extended past 6 h in patients who are at higher risk for or who may not tolerate bradycardia. Extended monitoring should include continuous overnight ECG monitoring (FDA, 2012). Higher risk patients are defined as those having severe bradycardia after administration of the first dose of fingolimod; those who have pre-existing conditions that may poorly tolerate bradycardia; those who have therapy with other drugs that may slow the heart rate or atrioventricular (AV) conduction; those who have QT interval prolongation prior to the first dose of fingolimod or at any time during cardiovascular monitoring; and those who receive drugs that may have drug interactions that could prolong QT interval and cause life threatening heart rhythm (FDA, 2012).

Our data provides examples of patients without pre-existing cardiac conditions, who were not on medication that affects cardiac conduction, and did not have a prolonged QTc at baseline, who developed cardiac arrhythmias following the first dose of fingolimod. These patients were considered low risk for the development of significant arrhythmias after first dose of fingolimod. Since the FDA's Drug Safety communication in May 2012, we have used continuous ECG monitoring for 6 h, as screening in all patients regardless of risk factors for arrhythmia. Our purpose is to familiarize physicians with our screening process and management for arrhythmias caused by the first dose of oral fingolimod.

2. Methods

This is a retrospective, single center study of 59 patients with clinically definite RRMS by McDonald criteria 2010 (Polman et al., 2010) who began fingolimod treatment (0.5 mg oral Gilenya®, Norvartis AG, Stein, Switzerland). All patients underwent continuous ECG monitoring for 6 h, hourly review of vital signs, standard 12-lead ECG at baseline and at the end of the 6-h period regardless of risk factors. At the end of the observation period, a cardiologist examined the patient and reviewed all the data before discharging each patient. In patients who developed symptoms or arrhythmia, monitoring was continued for an extended period. The authors are solely responsible for the design, analysis and editing of the paper and its final contents. The study was reviewed and approved by our institutional review board. This study was not sponsored and did not receive any intellectual contribution from a pharmaceutical or medical company.

3. Results

Three out of 59 patients (5%) developed rhythm disturbances that led to the discontinuation of the use of fingolimod. None of the patients had any history of cardiac disease or arrhythmia. None of the patients were taking medications that are proarrhythmic or affect the heart rate. Two out of three patients with rhythm disturbance had bradycardia secondary to atrioventricular conduction abnormality (3%) and one had sinus bradycardia with accelerated Idioventricular rhythm. The other 56 patients (95%) did not show any sign of bradycardia or symptoms during the 6 h observation period.

Our first patient is a 53 year old Caucasian male with a history of RRMS since 1993 who was treated initially with glatiramer acetate (20 mg subcutaneously every day; Copaxone® TEVA Pharmaceuticals Inc., North Wales, PA, USA) and then natalizumab (300 mg intravenous every 4 weeks; Tysabri®, Biogen Idec and Elan Pharmaceuticals, Cambridge, MA, USA), which was stopped after 70 doses due to John Cunningham virus (JCV) seropositivity and perceived lack of efficacy. He had a history of hypertension, which was well controlled with amlodipine/benzapril combination and hyperlipidemia treated with atorvastatin (10 mg oral every day; Lipitor® Pfizer, New York, NY, USA). He had no significant past cardiovascular history and was admitted to our outpatient observation unit for monitoring after the first dose of fingolimod. Initial vitals were as follows: heart rate 65 beats per minute, blood pressure 125/70 mmHg, respiratory rate 14 per minute, oxygen saturation by pulse oximetry 98% on room air. His cardiovascular examination was normal as well as his baseline ECG, which showed normal sinus rhythm with heart rate of 65 beats per minute, PR interval of 148 ms, QRS duration 82 ms, and QTc 399 ms.