Fingolimod is the first oral agent approved for the treatment of relapsing-remitting multiple sclerosis (RRMS). Fingolimod acts as a sphingosine-1-phosphate (S1P) receptor antagonist. S1P receptors are found on T and B cells, in heart, in the lungs and on the eye. The effects on the cardiovascular system have been well documented to be mostly bradycardia. In both phase III studies of fingolimod, a decrease in heart rate was noted after the first dose and peaked at 4 to 5 hours after administration. 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. No direct causality for sudden cardiac death has been established, but the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have revised prescription standards after the first dose of fingolimod. The FDA now recommends that all patients should be monitored for signs of a bradycardia for at least 6 hours after the first dose. Hourly pulse and blood pressure measurement and an ECG prior to dosing and at the end of the observation period are recommended.

**RESULTS**

Two out of 25 patients developed an arrhythmia that led to discontinuation of fingolimod. Our first patient is a 44 yo female with RRMS since 2002 who was tried on interferon β-1a IM, glatiramer acetate, alemtuzumab, as part of a clinical trial, and natalizumab. Nalulizumab was stopped due to JCV Ab seropositivity and a prior history of immunosuppression (alemtuzumab). The risk of progressive multifocal leukoencephalopathy (PML) was felt to be too high (11.1/1000 after 24 months). She had no prior history of cardiac disease and was admitted to our outpatient observation unit for monitoring. Initial vital signs were as follows: pulse 65 bpm, blood pressure 113/83 mmHg. Her cardiovascular examination was normal as well as her baseline ECG, which showed normal sinus rhythm at 63 bpm, with normal axis, PR interval 190 msec, QRS duration 82 msec and QTc interval of 424 msec. For the first 5 1/2 hours after receiving her first dose of fingolimod she did not show any evidence of arrhythmia while being continuously monitored by ECG. She then developed second-degree AV block, Mobitz type I (Figure 1). Her lowest heart rate was 54 bpm. Upon questioning, she admitted having a mild headache associated with dizziness once she stood up. She also attempted to ambulate but felt palpitations with mild syncope. She was given 0.5 mg intravenous atropine which resolved the second degree AV block type I and immediately, she was admitted for 24 hour observation. No other intervention was performed and no other arrhythmia was detected. Fingolimod was discontinued.

**RESULTS CONTINUED**

Our second patient is a 53 yo male with RRMS since 1993 who was treated initially with glatiramer acetate and then natalizumab, which was stopped after 70 doses due to JCV Ab seropositivity and perceived lack of efficacy. He had a history of hypertension, which was well controlled with amlopidine/azempril combination and hyperlipidemia treated with atorvastatin. He had no significant past cardiovascular history and was admitted to our outpatient observation unit. Initial vitals were as follows: pulse 65 bpm, blood pressure 125/70 mmHg. His cardiovascular examination was normal as well as his baseline ECG, which showed normal sinus rhythm with heart rate of 65 bpm, PR interval of 148 msec, QRS duration 82 msec, and QTc 399 msec. Telemetry showed sinus rhythm without arrhythmia or PR interval prolongation for the first 4 1/2 hours following the administration of fingolimod. Then frequent premature ventricular contractions occurred interspersed with normal sinus beats and he eventually went into sinus pause with ventricular escape rhythm for 45 seconds at a rate of 62 bpm (Figure 2). He was completely asymptomatic and denied any dizziness, chest pain, or shortness of breath. We decided not to continue with fingolimod therapy and continued telemetry monitoring for twenty-four hours. The patient did not have any further episodes of bradycardia, premature ventricular contractions or ventricular escape rhythm. Repeat ECG at the end of monitoring did not show abnormalities and serum electrolytes including potassium, magnesium and calcium were normal.

**CONCLUSION**

Our experience would suggest that further study may be needed regarding potential cardiac complications during use of fingolimod. We suggest considering continuous on-line electrocardiographic telemetry for monitoring for potential arrhythmias in patients starting on fingolimod. We also suggest considering an increase of the observation period >6 hours.

**REFERENCES**