Multiple Sclerosis and Related Disorders 5 (2016) 40–46

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Clinical trial

The management and outcomes of fingolimod first dose cardiac monitoring in UK patients with relapsing-remitting multiple sclerosis

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ARTICLE INFO

Article history:
Received 27 July 2015
Received in revised form
29 September 2015
Accepted 23 October 2015

Keywords:
Multiple sclerosis
Gilenya (fingolimod)
First-dose monitoring
Observational research
Retrospective chart review
UK

ABSTRACT

Background: Patients initiated on Gilenya (fingolimod) require cardiovascular monitoring for 6 h after the first dose. Novartis has engaged an independent provider (Regent's Park Heart Clinics [RPHC]) to provide a first dose observation (FDO) service to UK neurologists.
Objectives: To describe routinely-documented clinical observations (heart rate [HR], blood pressure [BP], cardiac rhythm [CR]) and outcomes from the RPHC fingolimod FDO service.
Methods: Pseudonymised data (clinical observations pre-dose and for 6 h after the first dose and any requirement for extended monitoring) were collected retrospectively from RPHC records for the first 850 RPHC FDO episodes (undertaken Jul-2012 to Jan-2015). All episodes involved patients with relapsing-remitting MS who were initiated on fingolimod in routine National Health Service (NHS) clinical practice.
Results: In 78% of FDO episodes the patient was female. Mean age at date of episode was 40.1 years. Mean HR was 72.7 bpm (beats per minute) pre-dose, 64.3 bpm at 5 h (the lowest recorded HR) and 66.1 bpm at 6 h post-dose. New-onset heart block was observed in 2% of episodes (1.5% first-degree; 0.5% second-degree). The patient was discharged at 6 hours post-dose in 97% of episodes and required extended monitoring in 3%. In 5 episodes overnight monitoring was required. There were no episodes in which the patient required pharmacological intervention or temporary cardiac pacing.
Conclusions: In this real-world UK population fingolimod initiation was predominantly uneventful; clinical observations were similar to previous clinical trials.

1. Introduction

Fingolimod (Gilenya, Novartis Pharma AG) is a daily oral sphingosine 1-phosphate receptor (S1PR) immunomodulator, approved in the European Union for use in patients with highly active relapsing-remitting multiple sclerosis (RRMS) who have failed to respond to at least one disease modifying therapy or patients with rapidly evolving severe RRMS (Novartis Pharmaceuticals UK Ltd., 2015). Fingolimod was the first oral treatment to be approved for RRMS. In two two-year Phase III studies, fingolimod reduced relapse rates by 48–71%[1] compared to placebo (Kappos et al., 2010; Calabresi et al., 2014). A one-year study showed a reduction in relapse rates by 52–61%[1] compared to beta interferon-1a (Cohen et al., 2010).

Owing to its mechanism of action (Brinkmann, 2009; Camm et al., 2014), initiation of fingolimod results in a decrease in heart rate (HR) and may be associated with atrioventricular (AV) conduction delays. These cardiac effects have been well characterised in the Phase III studies(Kappos et al., 2010; Calabresi et al., 2014; Cohen et al., 2010; DiMarco et al., 2014), which showed them to be mostly transient and asymptomatic in nature. The decrease in HR after the first dose starts within one hour and is maximal within 6 h, usually returning to baseline within one month. Conduction delays are typically asymptomatic, require no treatment and resolve within 24 h. The Phase IIIb open-label Fingolimod Initiation and cardiac Safety Trial (FIRST) (Gold et al., 2014), and the phase IV

Abbreviations: RRMS, relapsing-remitting multiple sclerosis; HR, heart rate; AV, atrioventricular; ECG, electrocardiogram; RPHC, Regent's Park Heart Clinics; FDO, first dose observation; UK, United Kingdom; NHS, National Health Service; BP, blood pressure; CR, cardiac rhythm; bpm, beats per minute; ms, milliseconds; REC, Research Ethics Committee; SD, standard deviation; mmHg, millimetres of mercury.

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[1] 48% and 52% reductions observed in the overall study population; 61% and 71% reductions observed in patients with highly-active disease despite prior beta interferon 1a.

http://dx.doi.org/10.1016/j.msard.2015.10.009

Evaluate Patient OutComes (EPOC) study (Hughes et al., 2014), which examined the short-term cardiac effects of fingolimod in patients that more closely resemble the real world population, observed similar effects.

To ensure that appropriate measures can be taken if adverse cardiac effects occur, patients initiated on fingolimod must have their heart activity monitored before the first dose and for at least 6 h afterwards, with monitoring extended for a further two hours (or overnight) in the event of very low (or decreasing) HR or electrocardiogram (ECG) abnormalities. The same first dose monitoring is required when treatment is interrupted for 1 day or more in the first 2 weeks, more than 7 days during weeks 3–4 or more than 2 weeks after 1 month of treatment (Novartis Pharmaceuticals UK Ltd., 2015). In March 2012, Novartis engaged an independent cardiac healthcare provider (Regent's Park Heart Clinics [RPHC]) to provide a fingolimod first dose observation (FDO) service to neurologists in the UK National Health Service (NHS). RPHC provide a network of clinical staff and clinicians to support NHS neurology departments in meeting the fingolimod FDO requirements. During each FDO episode RPHC staff routinely measure and document clinical observations (HR, blood pressure [BP] and cardiac rhythm [CR] according to a strict monitoring protocol).

We conducted a retrospective review of the care pathway documentation which is completed routinely by RPHC staff during each monitoring episode, for the first 850 episodes undertaken by the service. The objectives were to describe clinical observations (HR, BP and CR) and outcomes (requirement for extended monitoring or overnight admission) from the RPHC fingolimod FDO service. By reporting clinical observations during fingolimod initiation and FDO outcomes for a large cohort of patients, initiated on fingolimod in real world UK clinical practice, we hope to further improve understanding of the cardiac safety profile of fingolimod and increase the information available to UK neurologists to inform decision making.

2. Materials and methods

2.1. RPHC FDO protocol

The objective of the RPHC FDO service is to provide real-time cardiovascular monitoring during fingolimod initiation for up to 4 patients per session per day. The service was implemented in July 2012 and has now been implemented in 37 UK NHS hospitals; geographic spread is shown in Fig. 1. The FDO protocol used by RPHC is given in Fig. 2.

RPHC provide a cardiac physiologist or specialist cardiac nurse to visit sites together with all of the necessary cardiac equipment. A 12-lead ECG is performed at baseline and remotely reviewed by a RPHC consultant cardiologist before first dose administration and repeated 6 h post-dose. For 6 h after the first dose, patients are monitored continuously using a cardiac monitor which displays a real-time ECG trace (minimum 3-lead). BP and HR are measured and documented hourly. Patients whose HR is lowest at the 6 hour assessment point and those who experience bradyarrhythmia-related symptoms are recommended to have assessment extended for an additional 2 h and provision of overnight monitoring is considered during this extension period. Hospital admission under the appropriate NHS medical team is recommended for patients meeting one or more pre-specified criteria (e.g. requirement for pharmacological intervention, third-degree AV block during the monitoring period or HR less than 45 bpm at 6 h). Summary reports are provided to the NHS centre at the end of monitoring detailing all observations and occurrences of any cardiac-related symptoms. RPHC do not provide clinical management or decision making; in all cases the decision to initiate fingolimod is made by the treating neurologist.

Fig. 1. Geographic spread of UK NHS hospital Trusts supported by the RPHC FDO service.

2.2. Retrospective review of FDO outcomes

We conducted a retrospective review of the care pathway documentation which is completed routinely by RPHC staff during each FDO episode. FDO episodes were included in the review if the patient had a diagnosis of RRMS and was being initiated on fingolimod as part of routine NHS clinical practice (i.e. the decision to initiate fingolimod was made by their treating neurologist). Episodes relating to both treatment initiation and re-monitoring (following treatment interruption) were included. The first 850 eligible FDO episodes undertaken by RPHC were reviewed.

The retrospective review was undertaken by RPHC staff, who recorded data for each FDO episode on patient demographics; HR, BP and CR at baseline (pre-dose) and at hourly intervals thereafter, up to 6 h post-dose; baseline and 6 h ECG results; any requirement for extended monitoring or overnight stay and the reasons for this, and observations at 7–8 h post-dose (where available). Data were recorded in pseudonymised form and released to external researchers for independent analysis and reporting.

Before commencing the retrospective data collection, the lead neurologist at each NHS centre was contacted by RPHC and given the opportunity to discuss the activity and subsequent data dissemination plans. If any clinicians did not wish for data from their centre to be included, the relevant episodes from these centres would have been excluded; however, no such requests were made.