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Safety and efficacy of fingolimod in clinical practice: The experience of an academic center in the Middle East

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ABSTRACT

Background: Few published studies addressed real-world clinical experience with fingolimod especially in the Middle East region.
Objective: To review our clinical experience with fingolimod at a specialized academic MS center in Lebanon.
Methods: All patients treated with fingolimod at the MS Center between October 2011 and January 2015 were retrospectively identified.
Results: A total of 122 patients were included. The first dose observation was uneventful in 98.8% of patients. Annualized relapse rate decreased from 1.16 pre-treatment to 0.29 post-treatment representing a relative risk reduction of 75% ($p < 0.0001$). The proportion of patients with no new T2 or enhancing lesions was 66.3%. Seventy-six (62.3%) patients experienced adverse events with lymphopenia, increase liver enzymes, urinary tract infections and fatigue being the most common.
Conclusion: Our cohort confirms the effectiveness and safety of fingolimod in a real world setting.

1. Introduction

Multiple Sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system (Compston, 2006). The vast majority of patients with MS (approximately 85%) have a relapsing form at onset that progresses in the majority to a slowly secondary progressive course leading to accumulation of significant disability (Weinshenker et al., 1989; Tremlett et al., 2008; Yamout et al., 2008). Although no cure currently exists, the use of disease modifying therapies has changed the course of the disease. Studies (Noyes and Weinstock-Guttman, 2013; Gold et al., 2010; Comi, 2008; Rieckmann, 2005; Kappos et al., 2006; Jacobs et al., 2000; Comi et al., 2012; Comi et al., 2001; Comi et al., 2009; Jeffrey, 2015) have shown that early control of disease activity as evidenced by prevention of relapses and new magnetic resonance imaging (MRI) lesions has a beneficial effect on long term disability. Fingolimod is a sphingosine 1-phosphate (S1P) receptor modulator approved for the treatment of relapsing remitting multiple sclerosis (RRMS). It inhibits the egress of certain subpopulations of lymphocytes from lymph nodes, causing redistribution rather than depletion of lymphocytes (Chun and Hartung, 2010). This leads to reduced infiltration of potentially auto aggressive lymphocytes into the central nervous system (Mandala et al., 2002).The efficacy of fingolimod was demonstrated in two phase III clinical trials (Kappos et al., 2010; Cohen et al., 2010) by significant reduction in annualized relapse rate and MRI gadolinium-enhancing (Gd +) lesions compared to placebo (Klotz et al., 2011) and interferon beta (IFNB)-1a (Cohen et al., 2010). In the FREEDOMS trial (Kappos et al., 2010), it reduced annualized relapse rate (ARR) and risk of disability progression by 54% and 30% respectively compared to placebo. In the TRANSFORMS trial (Cohen et al., 2010), fingolimod reduced ARR by 50% but not risk of disability progression when compared to IFNB-1a once weekly. The most common adverse events observed in clinical trials were infections (including two fatal herpes virus infections), elevation of liver function tests (LFTs), headache, bradycardia, atrioventricular (AV) block, macular edema and lymphopenia (Kappos et al., 2010; Cohen et al., 2010).

Although fingolimod efficacy and safety are well-established in controlled trials, few published studies addressed real-world clinical experience with this drug especially in the Middle East region (Bergvall et al., 2014; Correale et al., 2015; Ziemssen et al., 2014; Al-Hashel et al., 2014; Hersh et al., 2014). Such information is important since controlled trials with strict inclusion criteria might not reflect the whole spectrum of MS patients seen in every day practice. In May 2011, fingolimod was introduced to the Lebanese Market and was included in the "MS Center practice guidelines for the treatment of MS" and regional guidelines (Yamout et al., 2015) as first-line therapy in RRMS patients with early aggressive course or those with contraindication to IFNB, needle phobia, or unwilling/unable to perform injections, and as second-line therapy in patients with suboptimal response to first-line disease modifying therapies (DMT).

The aim of this study was to review our clinical experience with fingolimod looking at different outcomes including efficacy and safety

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Table 1
Baseline characteristics (n = 122).

Age, mean ± SD	35.3 ± 9.9 years
Sex	• Male: n = 45 (36.9%) • Female: n = 77 (63.1%)
Disease duration[a], mean ± SD	7.4 ± 6.6 years
Duration of therapy, mean ± SD (min–max)	19.18 ± 11 months (1–48)
	• <6 months: n = 12 (9.8%) • 6–12 months: n = 29 (23.8%) • 12–24 months: n = 47 (38.5%) • >24 months: n = 34 (27.9%)
Number of relapses in the previous year, mean ± SD (min–max)	1.16 ± 0.9 relapses (0–5)
Baseline EDSS score, mean ± SD (min–max)	2.3 ± 1.5 (0–7)
Main reason for switching from other DMT to fingolimod	
o Lack of efficacy: n = 80 (74.1%) o Poor tolerance: n = 24 (22.2%) o JCV seroconversion: n = 1 (0.9%) o Prolonged therapy with azathioprin: n = 1 (0.9%) o Others: n = 2 (1.8%)	

[a] Time from first MS symptoms to start of fingolimod treatment.

in a real world setting at a specialized academic MS center (MSC) in Lebanon.

2. Methods

2.1. Study design

This was an observational retrospective review of a prospectively followed cohort at the American University of Beirut Medical Center (AUBMC) MS Center (MSC). The charts of all patients seen at the MSC between October 2011 and January 2015 were reviewed. Patients were included in the study if they fulfilled the following criteria: (1) age older than 18 years, (2) confirmed diagnosis of RRMS according to the 2010 McDonald criteria (Klotz et al., 2011), (3) treatment with fingolimod, and (4) at least 1 follow-up visit after initiation of fingolimod therapy.

Patients were prospectively followed at the MSC every 3–6 months for a full clinical evaluation and an expanded disability status scale (EDSS). An enhanced 3 Tesla brain MRI was performed every 6–12 months according to a standard protocol set by the MSC with pre-specified sequences, orientation, and slice thickness. MRIs were read by experienced neuroradiologists to determine the presence of new T2 or Gd + lesions. All relapses, EDSS, and adverse events were assessed by neurologists at the MSC either during regular or emergency visits in case of suspected relapse or adverse events. A relapse was defined as the occurrence of new or worsening of previously stable neurological symptoms suggestive of demyelination and supported by objective findings on physical examination, lasting for at least 24 h in the absence of infection or fever. Disability progression was defined as an increase in EDSS of at least 0.5 sustained for at least 3 months.

Patients performed pre-treatment baseline studies which included: complete blood count, liver function tests, varicella zoster antibody titer, pregnancy test in women with childbearing age, ophthalmologic exam, and electrocardiogram (ECG). Complete blood count and liver function tests were repeated at 1 and 3 months and the ophthalmologic exam at 3 months. All patients underwent first dose observation with hourly measurement of blood pressure and heart rate and an ECG at the end of the observation period.

The primary endpoint was the ARR defined as number of relapses per year. The secondary end points were: proportion of patients free of relapse, proportion of patients free of disability progression defined as an increase in the EDSS score of ≥0.5 score between baseline and last visit confirmed on 2 consecutive visits at least 3 months apart, proportion of patients free of Gd + lesions and new T2 lesions, and adverse event measures.

2.2. Data collection

After obtaining approval of the AUBMC Institutional Review Board, all patients presenting to the AUBMC MSC and prescribed fingolimod were identified. A retrospective medical record review was conducted and the following prospectively collected parameters were obtained: age, sex, disease duration, clinical course, number of relapses in the previous year, number of relapses on fingolimod therapy, pre and post treatment EDSS, previous treatments, MRI findings (new T2 or Gd + lesions), reason for switching to fingolimod, duration of fingolimod therapy, and fingolimod baseline screening studies (complete blood count, liver function tests, varicella zoster antibodies titer, pregnancy test in women with childbearing age, ophthalmic exam and electrocardiogram). Absolute lymphocytic counts and liver function tests were obtained one and three months after fingolimod initiation. First-dose observation data was extracted from the inpatient medical records and included vital signs, adverse events and interventions if any.

2.3. Statistical analysis

Data were analyzed using SPSS v20.0 for Windows (SPSS, Chicago, IL, USA). Descriptive analyses were carried out by calculating the number and percent for categorical variables, whereas continuous ones were presented as mean and standard deviation (SD). The Annualized Relapse Rate (ARR) in the pre-treatment period was calculated by determining the number of confirmed relapses in the year preceding treatment, while the ARR in the post-treatment period was calculated by dividing the number of confirmed relapses by the duration of treatment in years. The p-value for the difference in the two ARR rates was calculated using the paired t-test. Statistical significance was considered at a p-value of <0.05.

3. Results

3.1. Baseline characteristics

A total of 137 patients were identified from the MSC medical records of whom 15 were excluded because they lacked any follow-up after treatment initiation. Of the 122 patients included in the study, 77(63.1%) were women and 45(36.9%) men with a mean age of 35.3 ± 9.9 years and a mean disease duration of 7.4 ± 6.6 years. The mean duration of treatment with fingolimod was 19.18 ± 11 months, with 12 patients receiving therapy for less than 6 months, 29 between 6 and 12 months, 47 between 12 and 24 months, and 34 for more than 24 months. The mean baseline EDSS was 2.3 ± 1.5 and the mean ARR 1.16 ± 0.9 in the year preceding treatment initiation (Table 1).

Fingolimod was used as first line therapy in 11.5% and as second line therapy in 88.5% of our patients. Previous treatments were IFNB in 92 (75.4%) and other therapies in 16 (13.1%) patients including azathioprine (3), natalizumab (3), mitoxantrone (4), and others. Of the 92 patients who were switched from IFNB to fingolimod, 40.2% were treated with IFNB 1a subcutaneously three times weekly, 32.6% were on IFNB 1a once weekly and 27.2% were on IFNB 1b SC every other day. The main reasons for switching from other DMT to fingolimod were lack of efficacy in 80 (74.1%) patients, poor tolerance in 24 (22.2%), and fear of long-term side effects in 1 patient on natalizumab and positive JC virus serology, and another on azathioprine for more than 10 years (Table 1).

During pre-treatment screening 1 patient was found to have QT segment prolongation on ECG and congestive heart failure with an ejection fraction of 49% on echocardiography. Fingolimod was initiated in hospital under continuous cardiac monitoring. Another patient was