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Relapse rates in patients with multiple sclerosis treated with fingolimod: Subgroup analyses of pooled data from three phase 3 trials

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ABSTRACT

Background: Fingolimod is a once-daily, orally administered therapy for relapsing forms of MS. It has been shown to reduce relapse rates significantly in all phase II and phase III clinical trials when compared with placebo and intramuscular interferon β-1a (IFNβ-1a IM).

Methods: This study compared annualized relapse rates (ARRs) associated with fingolimod, placebo and IFNβ-1a IM, in patient subgroups from the pooled FREEDOMS, FREEDOMS II, and TRANSFORMS populations. This provided a large data set in which the efficacy of fingolimod could be assessed across a range of patient subgroups, including clinically relevant subgroups not previously analysed.

Results: Compared with placebo, fingolimod was associated with significantly lower ARRs across all patient subgroups with relative reductions in ARRs ranging from 35% (patients who had previously received treatment for their MS for up to 1 year; $P<0.05$) to 69% (patients with symptoms for less than 3 years before study entry; $P<0.001$). Other relative reductions in ARR compared with placebo included 64% in patients aged 40 years or younger and 63% in those naïve to treatment ($P<0.001$ for both). Compared with IFNβ-1a IM, the greatest benefits to ARR were seen in patients aged 40 years or younger (55% relative ARR reduction, $P<0.001$) and in a small subgroup of patients who had previously received IFNβ and glatiramer acetate (55% relative ARR reduction; $P<0.05$). Reductions in ARR compared with IFNβ-1a IM were not statistically significant in men (33%, $P=0.081$), in patients aged over 40 years (23%, $P=0.230$) and in those who had received treatment prior to the study for 1 year or less (35%, $P=0.108$). Fingolimod was associated with significantly lower ARRs compared with placebo and with IFNβ-1a IM irrespective of treatment status (treatment-naïve and previously treated for MS), and regardless of type of previous therapy.

Conclusions: Fingolimod provided consistent efficacy benefits over placebo and IFNβ-1a IM across a range of subgroups of patients with relapsing MS. The magnitude of the beneficial effect of fingolimod over IFNβ-1a IM may depend on age, sex, and duration of previous treatment. These findings suggest that most benefit will be gained by patients who start fingolimod early in the disease course, but the findings also suggest that fingolimod treatment will benefit patients later in the disease course when they have already accrued disability.

1. Introduction

Key therapeutic aims in relapsing–remitting multiple sclerosis (RRMS) are the preservation of neurological function and control of disease activity. Relapses are an important component of disease activity that impact patients' quality of life (Oleen-Burkey et al., 2012), and incomplete recovery from relapses is associated with step-wise accumulation of neurological disability (Lublin, 2007; Confavreux et al., 2003). Studies suggest that relapse frequency early in the course of MS correlates with long-term disability: follow-up of the pivotal 2-year trial of subcutaneous interferon (IFN) β-1b in patients with RRMS, found that increased annualized relapse rate (ARR) on study correlated with an increased likelihood of poor long-term physical outcomes at 16 years (Goodin et al., 2012). Similarly, breakthrough disease activity including relapses during 2 years of intramuscular (IM) IFNβ-1a

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therapy was associated with an increased risk of disability at 15 years (Bermel et al., 2013). In the shorter term, it has been shown that reductions in relapse rates associated with treatment contributed to reductions in disability progression at follow-up (Sormani et al., 2011; Sormani et al., 2015).

Fingolimod (Gilenya; Novartis Pharma AG, Basel) is a once-daily, orally administered therapy for relapsing forms of MS. It has been shown to reduce relapse rates significantly in phase 2 and phase 3 clinical trials when compared with placebo and IFNβ-1a IM (Cohen et al., 2010; Kappos et al., 2010; Kappos et al., 2010; Calabresi et al., 2014). In the 2-year, phase III FTY720 Research Evaluating Effects of Daily Oral Therapy in MS (FREEDOMS) and FREEDOMS II studies, fingolimod significantly reduced ARR compared with placebo (Kappos et al., 2010; Calabresi et al., 2014). In the 1-year, phase III Trial Assessing Injectable Interferon versus FTY720 Oral in RRMS (TRANSFORMS), ARR was significantly lower in patients treated with fingolimod than among those treated with IFNβ-1a IM (Cohen et al., 2010), and patients who switched from IFNβ-1a IM to fingolimod at the end of TRANSFORMS showed a significant improvement in ARR over the 1-year study extension period (Khatri et al., 2011).

Further analyses of the three individual phase III studies assessed the effects of fingolimod in prespecified patient subgroups (Cohen et al., 2013; Devonshire et al., 2012; Goodin et al., 2013). Subgroups were defined by age (≤ 40 or > 40 years), sex, treatment history (previously treated or treatment-naïve), and disease characteristics at baseline, including the number of previous relapses (0, 1, or ≥ 2 relapses in the previous 2 years), number of lesions (0, 1–2, or ≥ 3 gadolinium [Gd]-enhancing lesions), and the level of disability (Expanded Disability Status Scale [EDSS] score < 3 or ≥ 3) (Cohen et al., 2013; Devonshire et al., 2012; Goodin et al., 2013). In most of these patient subgroups in the three studies, fingolimod was associated with higher efficacy assessed by clinical and magnetic resonance imaging measures of disease activity, than placebo or IFNβ-1a IM.

The aim of the current paper is to present findings from subgroup analyses in a patient population pooled from FREEDOMS, FREEDOMS II, and TRANSFORMS. Pooling these patient populations provides a large data set, analysis of which may provide more insight than could be derived from individual study populations into the efficacy of fingolimod across a range of patient subgroups. In addition to those reported from the individual studies, this new analysis includes subgroups based on duration of symptoms prior to enrolment to provide further assessment of the impact of fingolimod relatively early in the disease course. Furthermore, insights into the efficacy of fingolimod when switching treatments is provided by analyses of subgroups based on prior treatment with IFN or glatiramer acetate (GA), and the duration of any prior treatment for MS. This subgroup analysis is especially important as in most countries fingolimod is registered as second line treatment after failure of injectable therapies.

2. Methods

2.1. Study design and patient population

This pooled analysis involved patients from FREEDOMS (NCT00289978), FREEDOMS II (NCT00355134), and TRANSFORMS (NCT00340834). The methods of all three studies have been published previously (Cohen et al., 2010; Kappos et al., 2010; Calabresi et al., 2014), and the analyses in this article do not involve new patients. All studies adhered to the International Conference on Harmonization Guidelines for Good Clinical Practice (ICH harmonised tripartite guidelines for good clinical practice E6(R1), 2015), and were conducted in accordance with the Declaration of Helsinki (World Medical Association, 2015). 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.

The studies involved patients aged 18–55 years with RRMS, diagnosed in accordance with the 2005 McDonald criteria (Polman et al., 2005), who had an EDSS score of 0–5.5 and one or more documented relapses in the previous year or two or more documented relapses in the previous 2 years. Exclusion criteria included relapse or corticosteroid treatment in the 30 days before randomization. In FREEDOMS and FREEDOMS II, patients had to have stopped IFNβ-1a or GA therapy at least 3 months before randomization to be included; in TRANSFORMS, recent therapy with IFNβ or GA was permitted.

In the double-blind FREEDOMS and FREEDOMS II studies, patients were randomized (1:1:1) to oral fingolimod 0.5 mg or 1.25 mg or placebo once daily for 24 months (Kappos et al., 2010; Calabresi et al., 2014). In TRANSFORMS, a double-blind, active-controlled study, patients were randomized (1:1:1) to oral fingolimod 0.5 mg or 1.25 mg once daily or IFNβ-1a IM at a weekly dose of 30 μg for 12 months (Cohen et al., 2010).

The primary efficacy endpoint in all studies was estimation of ARR, which was defined as the number of confirmed relapses during a 12-month period. Relapses were assessed by the examining neurologist within 7 days of onset. To qualify as a confirmed relapse, neurological symptoms had to be accompanied by an increase in EDSS score of ≥ 0.5 points or by an increase of 1 point in each of two EDSS functional-system scores or 2 points in one EDSS functional-system score (excluding the bowel–bladder or cerebral functional systems).

2.2. Analysis subgroups

Analysis subgroups were selected on the basis of previous studies that have shown certain factors to be potential predictors of clinical outcome in patients with RRMS (Scott et al., 2000; Confavreux and Vukusic, 2006; Bove and Chitnis, 2013; Losseff et al., 2001; Brex et al., 2002). The following subgroups were either prespecifed, or based on ones prespecified (see below), in the TRANSFORMS, FREEDOMS, and FREEDOMS II protocols: age (≤ 40 years or > 40 years; sex; treatment history (treatment-naïve or previously treated with any MS medication at any time before study entry); number of Gd-enhancing lesions (0 or ≥ 1); number of relapses in the 2 years before study entry (≤ 2 or ≥ 3); baseline disability (EDSS score 0–2.5 or ≥ 3). In these subgroups, ARR was estimated using a negative binomial model with study as a factor. The other subgroups examined were ones defined *post hoc* to explore in greater depth factors such as treatment history in the FREEDOMS and TRANSFORMS populations (Agius et al., 2014; Kremenchutzky et al., 2014), and which have identified subpopulations that may particularly benefit from fingolimod treatment: time from first MS symptom to study entry (< 3 or ≥ 3 years) (Agius et al., 2014); patients who had received injectable treatment for MS before study entry (IFN versus IFN-naïve, GA versus GA-naïve, IFN and GA versus naïve to either); and duration of previous treatment before randomization (0, ≤ 1, > 1–≤ 3, and > 3 years) (Kremenchutzky et al., 2014). In these subgroups, ARR was estimated using a negative binomial model with study, treatment, subgroup, and treatment-by-subgroup as factors.

In all three studies, modifications were made to some subgroup definitions after database lock (Cohen et al., 2013; Devonshire et al., 2012). The reasons for these modifications are explained in detail in a previous publication (Devonshire et al., 2012). Briefly, definitions were modified to harmonize the three studies, to ensure adequate patient representation, and to enable clinically meaningful comparisons. The categories for number of relapses