Longitudinal quantitative assessment of macula during therapy with fingolimod in relapsing-remitting multiple sclerosis

Longitudinal quantitative assessment of macula during therapy with fingolimod in relapsing–remitting multiple sclerosis

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Abstract

Purpose

Fingolimod is the first oral drug approved for treatment of relapsing–

remitting multiple sclerosis (RR-MS), and it has potential macular side effects. Despite the qualitative evidence of macular oedema under treatment, longitudinal quantitative assessment is lacking. To address this issue, we measured macular volume and central foveal thickness in a cohort of MS patients on fingolimod over 12 months of treatment.

Methods

Central foveal thickness (CFT) and total macular volume (TMV) were longitudinally recorded with spectral-domain optical coherence tomography in a cohort of 23 RR-MS patients treated with fingolimod at baseline, 3, 6 and 12 months. OCT parameters were analysed considering previous history of optic neuritis (ON). Comparison of means was performed with variance analysis (ANOVA).

Results

Macular oedema occurred in none of the patients. Comparing both groups of patients (with and without previous ON), no statistically significant difference was found during the follow-up both for CFT and TMV ($p = 0.99$ and $p = 0.96$, respectively) although a slight early but not significant TMV reduction was detected.

Conclusions

In our cohort, therapy with fingolimod did not cause any change in CFT and TMV in MS patients during a 12-month follow-up independent of previous ON.

Keywords

Multiple sclerosis
Optic neuritis
Fingolimod
Spectral-domain optical coherence tomography
Central foveal thickness
Total macular volume

Introduction

Multiple sclerosis (MS) is an immune mediated chronic inflammatory central nervous system (CNS) disease characterised by demyelination and axonal loss resulting in progressive disability [1].

The treatment of MS consists of immunomodulatory therapies with different mechanisms of action, routes of administration and risk–benefit profiles. In 2010, fingolimod was approved as first oral drug for the treatment of relapsing–remitting multiple sclerosis (RR-MS) based on positive results of two phase III clinical trials, FREEDOMS and TRANSFORMS, versus placebo and intramuscular interferon beta-1a, respectively [2, 3]. Fingolimod is a sphingosine 1-phosphate receptor (S1PR) modulator that, after phosphorylation, binds with high affinity to S1PR acting as a functional antagonist and leading to receptor internalisation into lymphocytes. This mechanism results in inhibition of egress of autoreactive lymphocytes from lymph nodes and their subsequent migration to CNS [2, 3].

During the two phase III clinical trials, some cases of macular oedema were recorded as adverse events in patients treated with fingolimod during the first months of treatment. In these clinical trials, macular changes were assessed by dilated ophthalmoscopy and OCT evaluating macular thickness only but not total macular volume (TMV), which is a more reliable quantitative measure. Moreover, previous history of optic neuritis (ON) was not considered [2, 3]. However, the real incidence of macular changes in the fingolimod-treated population is unknown. Long-term longitudinal studies with optical coherence tomography (OCT) investigating both central foveal thickness (CFT) and TMV during therapy as well as the occurrence of any change in these parameters are lacking. To address these issues, we present here the findings related to longitudinal assessment of CFT and TMV in MS patients under long-term treatment with fingolimod considering previous ON history as well.

Materials and methods

Twenty-three consecutive patients with RR-MS during treatment with fingolimod were recruited and followed for 12 months. All patients started fingolimod as second-line therapy according to the criteria approved by the Agenzia Italiana del Farmaco (AIFA). In particular, all patients suffered from a clinical relapse and showed at least one new active lesion at brain magnetic

resonance imaging (MRI) in the 12 months prior to start fingolimod treatment initiation. All patients gave their informed consent for the study. No patient was excluded, and the cohort was divided in two groups based on previous ON history (13 ON+ patients; 10 ON− patients). Clinical disability was assessed with the expanded disability status scale (EDSS) [4], MRI scans were performed at 1.5 T with a Siemens machine at baseline and after 12 months of treatment, and new gadolinium (GAD)-enhancing lesions were assessed. In both groups, SD-OCT (Cirrus 4000 SD-OCT; Carl Zeiss Meditec, Inc, Dublin, CA) was performed at baseline, 3, 6 and 12 months recording CFT and TMV. Macular scans were obtained with the Macular Cube 512 × 128 mode, and mean CFT and TMV values were automatically calculated by the SD-OCT machine and automatically compared to reference values from an age- and sex-matched population included in the software. The scans were performed by investigator MC and checked by investigator MF blindly to previous history of ON as well as to neurological features. Mean values of both eyes were recorded and expressed as mean ± standard error. Comparison of mean values was performed with variance analysis (ANOVA test), while comparison of mean values between ON-positive and ON-negative groups and MRI findings at baseline and at 12 months was performed with unpaired *t* test. Correlation of CFT values with the number of MRI GAD^+ lesions was performed with Spearman *r* calculation. *p* values < 0.05 were considered significant. Statistical analysis was performed by the GraphPad Prism 7.02 software, CA, USA. Best-corrected visual acuity (BCVA) was measured at baseline and 12 months.

Results

The baseline demographic and clinical characteristics as well as longitudinal clinical and neuroradiological features of the patients are listed in Table 1. In our cohort, no cases of macular oedema were found. Considering all patients independently of the presence of previous ON, no statistically significant change was found during follow-up neither for CFT nor for TMV ($p = 0.99$ and $p = 0.96$, respectively). When analysing patients based on previous ON history, no statistically significant difference was found for CFT at baseline ($p = 0.50$) and at the end of follow-up ($p = 0.74$). With regard to TMV, a mean decrease of 0.065 mm^3 was found at 3 months in all patients ($p = 0.05$) remaining stable until 12 months. When adjusting for the presence of previous ON, a statistical trend towards lower mean values of TMV at baseline was found in patients with previous ON compared with the ON-negative group ($p = 0.07$). This trend was confirmed at the end of follow-up as well ($p = 0.08$) (Table 2). Mean BCVA at

T0 was 0.89 (SE 0.049) in the ON-positive group and 0.96 (SE 0.030) in the group without ON; at T12 mean BCVA was 0.91 (SE 0.040) in the ON-positive group and 0.97 (SE 0.022) in the ON-negative group. The average disability score remained unchanged at baseline and after 12 months of therapy (Table 1). There was no correlation between CFT values and MRI findings at baseline ($r = -0.04$; $p = 0.85$) as well as at 12 months ($r = 0.20$; 0.34). In particular, while a statistical trend towards a decrease in the new GAD^+ lesions was found at 12 months ($p = 0.06$) (Table 1), CFT and TMV values were unchanged.

Table 1

Baseline demographic and longitudinal clinical and radiological features of the patients

	T_0	T_{12}	*P*
Gender, *n* (F/M)	16/7	16/7	n.a.
Age (years)	41.9 ± 1.7	n.a.	n.a.
Disease duration (years)	16.4 ± 1.7	n.a.	n.a.
Disability (EDSS)	2.6 ± 0.4	2.5 ± 0.3	0.89
MRI GAD^+ lesions	1.14 ± 0.4	0.27 ± 0.2	0.06
T_0 baseline time, T_{12} 12 months treatment, *F* female, *M* = male, *n* = number of subjects, MRI GAD^+ = magnetic resonance imaging gadolinium enhancing lesions, *n.a.* not applicable. The results are shown as mean ± SEM			

Table 2

Demographic characteristics and SD-OCT data of patients with and without ON

Groups	**Sex M/F**	**Age, years SD**	**Mean CFT T_0 ± SE**	**Mean TMV T_0**	**Mean CFT T_3**	**M T_3**
ON (*n* = 13)	5/8 *n* = 13	41.54 ± 8.4	259.81 ± 3.82	9.508 ± 0.12	260.46 ± 3.81	9.
No ON (*n* = 10)	2/8 *n* = 10	42.58 ± 8.67	254.7 ± 4.25	9.89 ± 0.17	255.4 ± 4.61	9.
Total (*n* = 23)	7/16 *n* = 23	41.96 ± 8.26	257.5 ± 3.82	9.674 ± 0.10	258.3 ± 3.99	9.

Discussion

Fingolimod has been rarely associated with the development of retinal volume alterations, in particular with increase in macular volume [6] and macular oedema [2, 3]. Macular oedema consists of extracellular accumulation of fluid in the fovea as a consequence of the blood-retinal barrier (BRB) breakdown probably due to inflammation or dysfunction of astrocytes and neuronal precursor cells. Based on the fingolimod anti-inflammatory and perhaps neuroprotective properties, it is reasonable to hypothesise that the pathogenesis of fingolimod-related macular oedema is different from that observed in ophthalmological disorders but it has not been clarified yet. Activation of S1PR at the BRB by fingolimod resulting in alteration of the normal barrier function and consequent macular oedema has been suggested as a pathophysiological mechanism [7]. The gold-standard instrumental examination to detect macular oedema is OCT, a noninvasive method frequently used as a tool for assessing axonal loss in MS. Indeed, this examination reveals a reduction of macular volume and retinal nerve fibre layer (RNFL) in MS patients over the disease course [8]. An increase in macular volume by a mean of 0.025 mm^3 in 30 MS patients treated with fingolimod over a mean follow-up time of 5 months has been reported, while macular volume did not significantly change over a mean follow-up time of 6 months when compared to a paired MS control group never treated with fingolimod [6]. In the FREEDOMS trial, macular oedema was diagnosed in seven patients out of 429 (1.6%) receiving 1.25 mg of fingolimod and in none of the 425 patients treated with the approved dosage of 0.5 mg [2]. In the TRANSFORMS trial, macular oedema was diagnosed in six patients, four of the 420 (1%) receiving 1.25 mg of fingolimod and two of the 429 patients treated with the approved dosage of 0.5 mg (0.5%) [3]. Based on these evidences, a complete ophthalmologic examination 3–4 months after therapy initiation is strongly recommended in all patients and a preliminary complete ophthalmologic examination should be performed in patients with history of uveitis and diabetes mellitus [9]. In these two phase III clinical trials, macular changes were assessed by dilated ophthalmoscopy and OCT evaluating only macular thickness but not TMV [2, 3]. Although in these trials macular oedema was detected after several months of therapy, a case of acute onset fingolimod-associated macular oedema was recently reported in a 42-year-old white male subject with RR-MS, 24 h after fingolimod therapy initiation [10, 11]. In our longitudinal study over 12 months of treatment with fingolimod, no case of fingolimod-induced macular oedema was found in MS patients with or without previous ON. We did not find any correlation between CFT and TMV values and the number of MRI GAD^+ lesions, further supporting the efficacy of the

drug in reducing active brain lesions with no effect on macular parameters. However, the slight but not significant reduction of TMV in ON-positive compared to ON-negative patients is consistent with previous finding of MS-related reduction in macular volume [5,8]. Moreover, in our cohort, fingolimod did not cause any asymptomatic macular change in CFT and TMV during the follow-up, independently of previous ON. We were unable to confirm the modest increase in TMV found in a previous study over a follow-up time of 5 months [6]. This discrepancy may rely on different clinical characteristics of the cohorts in terms of age, disease duration, as well as disability. Our study assessing both CFT and TMV adds to the relative safety of fingolimod in terms of ocular side effects during treatment in MS patients. However, to rule out the occurrence of any ocular adverse event, a constant periodical ophthalmologic monitoring is required.

Compliance with ethical standards

Conflict of interest This is an independent work not supported by any sponsor. The authors have no financial interest regarding the content of this paper.

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