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Clinical activity after fingolimod cessation: disease reactivation or rebound?

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Abstract

Objective. There is debate as to whether the apparent rebound after fingolimod discontinuation is related to the discontinuation itself, or if it is due to the natural course of highly active multiple sclerosis (MS).

We aimed to survey the prevalence of severe reactivation and rebound after discontinuation of fingolimod in a cohort of Italian patients with MS.

Methods. Patients with relapsing-remitting MS (RRMS) who were treated with fingolimod for at least 6 months and who stopped treatment for reasons that were unrelated to inefficacy were included in the analysis.

Results. A total of 100 patients who had discontinued fingolimod were included in the study. Fourteen patients (14%) had a relapse within 3 months after fingolimod discontinuation, and an additional 12 (12%) had a relapse within 6 months. According to this study's criteria, 10 patients (10%) had a severe reactivation. Among these patients, 5 (5%) had a reactivation that was considered to be a rebound.

Conclusions

The present study showed that more than 26% of patients are at risk of having a relapse within 6 months after fingolimod discontinuation. Nevertheless, the risk of severe reactivations and rebound that we found is lower than that which has been previously described.

Introduction

Fingolimod was the first oral treatment to become available for multiple sclerosis (MS). In Europe, its use is indicated for aggressive forms of relapsing-remitting (RR) MS. Data from clinical trials showed that annualized relapse rates (ARR) were more than 50% lower in subjects taking oral fingolimod as compared to subjects taking placebo [1,2]. Since 2012, several reports have described a "rebound syndrome" after fingolimod discontinuation [3,14]. There is not a shared definition of "clinical rebound syndrome"; the most widely used definition is "a disease reactivation which surpasses the pretreatment activity level," especially with regard to ARR [15,16]. The concept of "rebound" after discontinuation of treatment was first proposed for natalizumab, a monoclonal antibody approved in 2006 to

treat the aggressive course of MS [17]. To date, only one study has explored the frequency of this phenomenon in patients with MS who discontinued fingolimod use. In this study, a clinical rebound syndrome was detected in 5 out of 46 subjects of a small cohort of patients who were referred to a single site (10.9%) [18]. However, a recent post-hoc analysis of the Phase III, placebo-controlled FREEDOMS and FREEDOMS II trials did not find any difference in the emergence of clinical rebound between patients treated with fingolimod and placebo [16]. To note, the minimum time of exposure of the patients evaluated in that post-hoc analysis was 3 months, and a so short exposure may less likely to cause a rebound. In addition, the FREEDOM trials collected MRI data post fingolimod discontinuation only for 3 months, and the subjects included in the rebound analysis are a small fraction of those enrolled.

While there is agreement in the literature that there is a high risk of rebound after natalizumab discontinuation [17], the concept of rebound after fingolimod cessation is less well defined.

The aim of this multicenter study was to evaluate the presence of clinical rebound syndrome after fingolimod discontinuation in a cohort of Italian patients with MS.

Materials and methods.

The patients who were enrolled in this study were recruited from 14 Italian MS centers between March and October 2017, after signed informed consent. The study was approved by the local ethics committees. The inclusion criteria were as follows: diagnosis of RRMS according to the McDonald criteria, previous treatment with fingolimod for at least 6 consecutive months over the person's lifetime, an absence of relapses in the last 6 months of treatment with fingolimod, and suspension of fingolimod due to reasons other than inefficacy (i.e., desire to become pregnant, side effects, self-discontinuation). In following the Italian Agency of Drug (AIFA) dispositions, all subjects started fingolimod due to aggressive disease from the onset (naïve patients), inefficacy of first-line treatments (switching patients), or a high risk of progressive multifocal leukoencephalopathy (PML) during natalizumab therapy. At each center from which patients were recruited, a neurologist with expertise in MS diagnosis and treatment collected the following demographic and clinical information from the patients' data records: gender; year of birth; age at onset; comorbidities; the last disease modifying drug (DMD) before fingolimod and the first DMD after its discontinuation; reason for suspension of fingolimod; ARR before, during, and after fingolimod; and Expanded Disability Status Scale (EDSS) score at the time that fingolimod was started and stopped, as well as during the post-suspension relapses.

A severe reactivation was defined as a relapse with an associated EDSS increase of at least 2 points or as 2 or more relapses in the 6 months following fingolimod discontinuation. A rebound was defined when a so high clinically severe reactivation, as previously described,

was never reported in patient's lifetime before fingolimod discontinuation. Thus, if the patient experienced the same severe disease activity both after fingolimod cessation and before (in any period of the course of the disease), that reactivation was not considered a rebound.

Statistical analysis

Quantitative results are presented as mean and standard deviation (SD) or median with the interquartile range (IQR). Absolute counts and percentages are reported for counts and binary variables. To evaluate demographic and clinical features as possible prognostic factors for severe reactivation after discontinuation of fingolimod, comparisons between patients with and without a severe reactivation were made using an independent samples Student's t test (age at first dose of fingolimod), a non-parametric Mann-Whitney U test (disease duration at first dose of fingolimod, duration of fingolimod treatment, EDSS score at fingolimod discontinuation, and ARR in the year before fingolimod initiation), and a chi-square test (gender and comorbidities). A p-value of <0.05 was considered statistically significant. Statistical analyses were performed with Stata (v.14; StataCorp) software.

Results

A total of 100 patients, 80 female (80%) and 20 male (20%), were included in the study. The mean age at onset was 27 years (SD: 8.7). At the time that fingolimod was started, the median EDSS and the mean duration of the disease were 2 (IQR: 1.5-3.5) and 10.7 (SD: 6.8), respectively. The median EDSS at the end of the treatment was 2 (IQR: 1-3.5). The mean duration of fingolimod treatment was 1.9 years (SD: 1.5, range: 0.5-5.9).

The vast majority of patients (70, 69.3%) started fingolimod therapy due to inefficacy of the first-line treatment, whereas 26 (25.75%) switched from natalizumab due to the high risk of PML and 5 (4.95%) had an aggressive course of the disease and were naïve to DMDs. The reasons for discontinuation of fingolimod were side effects or adverse events in 57 patients (57%), the desire to become pregnant in 33 patients (33%), and the patient's choice in 10 patients (10%).

After fingolimod, a new DMD was started in 72 patients within a median time of 3 months (IQR: 1.1-6.1). Sixty subjects did not experience any relapse after fingolimod discontinuation during the whole follow-up. Of them, 40 started a new DMD after a mean time of 5 months (IQR: 0.9-4.8). The ARR before, during, and after fingolimod regarding the whole cohort of patients is shown in figure 1.

Forty subjects had a relapse during the follow-up. In particular, 14 out of 100 patients (14%) had a relapse within 3 months after fingolimod discontinuation (only 1 started a new therapy within 3 months from the time that fingolimod was discontinued), and an additional 12 patients (12%) had a relapse within 6 months (5 started a new therapy within 6 months from the time that fingolimod was discontinued). According to the above-mentioned criteria, 10

patients (10%) had a clinically severe reactivation. Among them, 1 had a relapse associated with an EDSS increase of 6 points, 2 had a relapse associated with an EDSS increase of 3.5 points, 2 had a relapse associated with an EDSS increase of 2 points, and 5 had at least 2 relapses over 6 months. Upon analysis of the patients with severe reactivation, 5 of them (5% of the whole cohort) were defined as having had a clinical rebound. The demographic and clinical features of patients who experienced severe reactivation and rebound of the disease after discontinuation of fingolimod are reported in table 1.

From the analysis of clinical and demographic features, we were not able to detect significant prognostic factors for severe reactivation of disease. However, patients with a severe reactivation were younger and all were female. The detailed results are presented in table 2. The details about EDSS course, new and enhancing lesions on the brain MRI, and features of clinical reactivation are reported in the table 3.

Discussion

We conducted a retrospective, observational, real-life study involving a cohort of MS patients who were treated with fingolimod and who discontinued therapy for reasons other than poor efficacy. According to AIFA dispositions, when fingolimod was started all of the patients had an aggressive disease course, defined either as at least one relapse during interferon beta or glatiramer acetate treatment, or at least 2 relapses in the last year if the patient was not taking a DMD. Moreover, the patients' disease was stable during treatment, and the treatment was discontinued for side effects, the desire to become pregnant, or reasons other than inefficacy. In our cohort, 10% of patients experienced a severe reactivation of MS, and the reactivations of half of these patients met the definition of clinical rebound syndrome. As proposed in the recent analysis of the FREEDOMS and FREEDOMS II trials [16], patients experiencing a severe reactivation after discontinuation of fingolimod may simply have had a high level of MS activity, as compared to their pre-fingolimod clinical histories, which would be expected as part of the natural, unpredictable course of the disease.

It is worth noting that some of the clinical case studies that have described a rebound after fingolimod discontinuation [6-9,13], including the small cohort that was described by Hatcher et al [18], studied patients in which fingolimod was discontinued due to a lack of efficacy. Given that these patients did not respond to fingolimod, a reactivation of the disease would be expected upon therapy discontinuation. Recently, a high relapse rate and a low EDSS score before fingolimod treatment have been hypothesized to be negative prognostic factors for severe disease reactivation within the first 3 months after cessation of the therapy [19]. In our study, we were not able to identify factors that were strongly associated with severe reactivation after discontinuation of fingolimod. It is important to note, however, that all the patients with severe reactivation were female and were also younger than the other subjects, despite the fact that these differences did not reach statistical significance. This may have been due to the low statistical power of these comparisons.

Currently, there is no agreement on the pathological explanation for the supposed rebound. It is possible that it is related to a rapid lymphocyte reconstitution [18], but such a reconstitution has not been observed in all patients with a rebound. A more likely hypothesis is that a differential lymphocyte subset repopulation may be driving the rebound syndrome [20]. Moreover, it has been shown in the experimental model of MS, that rebound after fingolimod discontinuation is preceded by an overexpression of S1P1 in lymphocytes entrapped in lymph nodes, and it correlate with their massive egress from lymph nodes and with infiltrates in the Central Nervous System [21].

One important limitation of this study is that rebound was considered only on the basis of clinical, but not radiological, features. This is due to the observational and retrospective design of this study, in which data collected in clinical practice was analyzed. MRI examinations were not homogeneously performed across centers, both in terms of imaging protocols and in terms of timing of the scanning, and only a few patients underwent an MRI examination within the first 6 months after fingolimod discontinuation. Of note, clinical and radiological rebounds were considered as two separate entities in the analysis of the FREEDOMS and FREEDOMS II studies [16]. Another limitation, due to the fact that it is a real life study, is the lack of lymphocyte subset after fingolimod discontinuation for the vast majority of patients. That being said, the cohort of patients included in this study was selected from specialized Italian MS centers that belong to the research group iMUST. Given their participation in iMUST, these centers share relatively homogeneous rules for MS treatment and for strict observation of AIFA dispositions. In accordance with these prescriptive rules, only patients who fail a first line treatment, and those with aggressive course of MS from the onset of the disease could take fingolimod. Thus, all the patients had an aggressive course before the fingolimod initiation.

In conclusion, the rate of rebound after fingolimod discontinuation was estimated to be 5% in this relatively large case series, which is a lower risk than that which was previously described in another real-life cohort [18]. These data could have an important impact in the physician-patient communication, both when fingolimod is proposed as new therapy, and when it has to be stopped due to any kind of reason. Moreover, even if the risk emerged from our study is not so high as previously described, it has to be considered every time when fingolimod is discontinued. To confirm our results, it could be important to conduct other real-life studies analyzing the impact of clinical, and possibly, radiological rebound after fingolimod cessation in RR MS patients without disease activity before the discontinuation.

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Table 1

Demographic and clinical features of patients who experienced severe reactivation of disease after fingolimod discontinuation.

Pt: patients; IFN: interferon beta; nat: natalizumab; GA: glatiramer acetate; AE: adverse event; fingo: fingolimod

Pt	Rebound	Gender	Age at onset	DMD pre fingo	Relapses 12 months before fingo	MRI before fingo: new T2	MRI before fingo: Gd+	Comorbidity	Washout pre fingo (months)	Disease duration at fingo start (years)	EDSS at fingo start	EDSS at fingo stop	EDSS during reactivation	Reason for suspension	Lymphocytes after suspension	Time to lymphocytes count after suspension (months)	DMD post fingo	Time to new drug (months)
1	yes	Female	20	nat	0	no	no	none	5	5	1	2	2.5	Pregnancy	1200/ul	2	alem	3.7
2	yes	Female	25	nat	1	not available	not available	stroke	7	14	5.5	5	8.5	Pt decision	not available		none	
3	yes	Female	14	nat	0.81	no	no	none	7	16	3	3	9	Pregnancy	1100/ul	7	DMF	5.9
4	yes	Female	21	IFN	1.5	yes	yes	epilepsy	1	4	1.5	2	4	AE	not available		nat	8.1
5	yes	Female	26	nat	0	no	no	none	6	12	2	2	3	AE	2140/ul	0	nat	5.0
6	no	Female	24	IFN	2	no	no	headache	2	21	2.5	2.5	3	AE	1160/ul	1	IFN	2.9
7	no	Female	25	IFN	1	not available	not available	none	0	13	1	1	2	Pregnancy	not available		GA	0.8
8	no	Female	28	GA	0.84	no	no	none	2	13	3.5	4	6	Pt decision	1210/ul	0	terifl	0.6
9	no	Female	14	nat	2	yes	yes	none	6	7	1.5	0	2	AE	1289/ul	3	GA	3.7
10	no	Female	20	nat	0	not available	not available	none	4	6	2	1	4.5	AE	1000/ul	0	ritux	2.3

Table 2.
Demographic and clinical features in patients with no severe reactivation, with severe disease reactivation, and with rebound.

ARR: annualized relapse rate; EDSS: Expanded Disability Status Scale

	No severe reactivation (n=90)	Severe reactivation (n=10)	Rebound (n=5)
Age at first dose of fingolimod, mean (SD); range	38.2 (10.2); 18-60	32.9 (8.4); 21-45	31.6 (6.9); 25-39
Female, n(%)	70 (77.8)	10 (100)	5 (100)
Disease duration at first dose of fingolimod (years), mean (SD); median (25^{th}-75^{th})	10.6 (7); 8.7 (5.1-15.2)	11.3 (5.5); 12.2 (5.6-14.5)	10.5 (5.5); 12 (5.3-14.5)
Duration of fingolimod treatment (months), mean (SD); median (25^{th}-75^{th})	25.5 (13.1); 25.9 (18-28.9)	22.6 (17); 18.3 (10.7-30.1)	26.5 (13.1); 18.2 (18-39)
Comorbidities pre-fingolimod, n(%)	51 (56.7)	6 (60)	2 (40)
ARR before fingolimod, mean(SD)	0.87 (0.77)	0.92 (0.76)	0.66 (0.65)
EDSS at fingolimod cessation, median (25^{th}-75^{th} percentile)	2 (1-3.5)	2 (1-3)	2 (2-3)

Table 3

EDSS course, and MRI and reactivation features in patients who experienced a rebound.

Pt	EDSS before fingolimod	EDSS at the end of fingolimod	EDSS during the reactivation	MRI new T2 lesions	MRI Gd+ lesions	Type of reactivation within 6 months from discontinuation
1	1	2	2.5	yes	yes	2 relapses
2	5.5	5	8.5	yes	yes	2 relapse and EDSS increase > 2 points
3	3	3	9	yes	yes	one relapse with EDSS increase > 2 points
4	1.5	2	4	yes	yes	2 relapse and EDSS increase > 2 points
5	2	2	3	yes	yes	3 relapses

Figure 1.

Representation of the annualized relapse rate (ARR) before, during, and after fingolimod in three groups of patients: those without relapses after fingolimod discontinuation, those who experienced reactivation, and those who experienced a rebound of the disease.