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Fingolimod for the treatment of multiple sclerosis in French West Indies, a real-world study in patients from African ancestry

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ABSTRACT

Affecting 2.5 million people worldwide, multiple sclerosis (MS) is one of the main causes of acquired disability among young adults. In French West Indies (FWI), where MS has arisen from the end of the 80's, a low therapeutic response to interferons beta1 (IFN beta1) in patients of African descent, restrains the therapeutic options. Fingolimod is a Sphingosine-1-Phosphate receptor modulator whose efficacy in the treatment of MS has recently been shown in three phase III studies. Nevertheless, data are currently lacking concerning the use of Fingolimod among populations of African descent, particularly in a real-world setting.

Efficacy and safety information collected during the first two years of follow-up have been analysed retrospectively for all patients in whom Fingolimod treatment was introduced in FWI between its marketing date and December 2015.

Fifty-two consecutive patients with a relapsing remitting MS started Fingolimod therapy in the FWI, according to the European guidelines. After 24 months, 40 patients were still receiving the treatment. The average Annualized Relapse Rate (ARR) dropped by 81%, and 72.5% of patients remained free from disability progression during the 24 months on Fingolimod. MS remained controlled (according NEDA 3 criteria) for 41% of patients who were still on therapy at 24 months. Nine participants presented with a moderate or major side effect.

Unlike IFN beta1 therapy, Fingolimod appears to be effective in Afro-Caribbean patients in a real-world setting with a similar benefit to what has been observed in phase III studies in more selected populations.

1. Introduction

Few data are currently available regarding the use of Fingolimod in populations of African descent with multiple sclerosis (MS). A subgroup analysis from the phase III FREEDOMS-II trial involving 77 African-American (AA) subjects split into 3 groups (Fingolimod 0.5 mg per day (n = 24), Fingolimod 1.25 mg per day (n = 25), and placebo (n = 28)) respectively showed a 29% and a 54% reduction in the annualized relapse rate (ARR) with 0.5 mg and 1.25 mg of Fingolimod per day, compared to placebo [1]. Similarly, an effect on radiological activity was observed with a decrease in both frequencies of lesions taking Gadolinium (27%) and, new lesions T2 (77%) compared to placebo in the group receiving 0.5 mg. Nevertheless, these data were limited to only 19 patients. Finally, disability progression and the overall (clinical and radiological) MS activity with Fingolimod were not documented [1]. Satisfaction with treatment was emphasized in two phase IV studies involving 67 and 71 AA patients respectively [2,3]. These studies showed better adherence to Fingolimod treatment compared with first-line treatments (interferons beta1 (IFN beta1), Glatiramer Acetate). However, this may not directly reflect treatment efficacy [2,3].

Currently, available data suggest that IFN beta1 are less effective on MS in patients of African descent, while disease course appears more aggressive [4–6]. Further data on the real efficacy of very active treatments such as Fingolimod in this population are necessary. In addition, if AA and Afro-Caribbean (AC) MS patients share similarities (association with HLA DRB1 * 15:03, lesser response to IFN Beta1) [7–10], some environmental factors that may affect disease course or therapeutic response (climate, infections, or lifestyle-related factors) could vary between these two groups. More specific studies assessing Fingolimod use in the Caribbean population are therefore required. Analysing data from FWI patients brings the opportunity to assess Fingolimod efficacy and tolerance in real-world setting. In this study,

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we thus aim to assess MS activity using the composite NEDA-3 (No Evidence of Disease Activity) criteria through per protocol and survival analysis.

2. Material and methods

We conducted a multi-center retrospective pilot study, involving three main care centres in Martinique and Guadeloupe: Academic Hospital of Guadeloupe, Clinique de Choisy in Guadeloupe, and Academic Hospital of Martinique. All patients meeting the revised criteria of Mac Donald 2010 of RRMS, above 18 years old, living in the FWI, and, who initiated 0.5 mg daily Fingolimod therapy in accordance with European guidelines between March 2012 and December 2015 were eligible. Given the recent expansion of demyelinating diseases of the central nervous system from neuromyelitis optica spectrum disorder (NMOSD) to conventional MS in FWI, a peculiar attention was paid to exclude NMOSD including minor forms and overlapping syndromes.

Disease related data and patients' characteristics were prospectively collected from medical records and entered in the European Database for MUltiple Sclerosis (EDMUS 5.2.1) during follow-up. These data included: age at Fingolimod therapy initiation, age at diagnosis, sex, disease duration, ARR over 12 months and over 24 months prior to Fingolimod initiation, and, expanded disability status scale (EDSS) when treatment was started. Previous therapies and reasons for initiation of Fingolimod were also collected. Baseline cerebral and spinal cord MRI was performed between three months prior and one month after Fingolimod was started. Gadolinium-enhanced lesions as well as T2 lesion burden (a high lesion burden was defined by the presence of > 9 visible lesions on T2 weighted MRI) were assessed. The MRI protocol used at the outset and during follow-up corresponded to the Observatoire Français de la Sclérose En Plaques (OFSEP) protocol (MRI GE 1.5 Tesla in Martinique and MRI Siemens 1.5 Tesla in Guadeloupe).

A consultation was conducted at 3 months, 6 months and then every 6 months to assess biological and clinical tolerance, to look for possible relapse, and to determine the level of disability on the EDSS scale. Relapse was defined by the onset of new neurological symptoms or worsening of pre-existing symptoms, in the absence of fever. Symptoms should persist for at least 24 h; appear at least one month after the prior relapse, and result in a minimum increase of 0.5 point on the EDSS. The ARR was calculated after one and two years of Fingolimod therapy. Time from Fingolimod initiation to the first relapse was collected. The EDSS was determined at each visit. Disability progression was defined as a permanent worsening on EDSS scale over 6 months, and consisted in a 1 point increase for baseline EDSS between 0 and 5.5 and in a 0.5 point increase for baseline EDSS of 6 and above. Cerebral and cord MRI was performed after 12 and 24 months under therapy. New T2 hyperintensities and new gadolinium-enhanced lesions were investigated.

Significant adverse events were identified, including uncontrolled arterial hypertension, transaminases elevation > 3 times the upper limit of normal, neoplasia, severe infection (requiring hospitalization), lymphopenia under 200 g/l, the need for prolonged cardiac monitoring beyond 6 h, cessation of treatment for intolerance, and, unexpected pregnancy under treatment.

Treatment was interrupted in case of serious adverse event: symptomatic cardiac event during the first administration, lymphopenia under 200 g/l, elevation of transaminases > 5 times the upper limit of normal, macular oedema, major infection (especially Progressive Multifocal Leukoencephalitis (PML), Varicella-Zoster Virus, Herpes Simplex Virus and cryptococcal meningitis), neoplasia (including lymphomas and skin carcinomas).

Statistical analysis. The primary outcome was the rate of patients fulfilling No Evidence of Disease Activity: absence of relapse, disability progression, and, new T2 and/or gadolinium-enhanced lesions over 24 months under Fingolimod therapy (NEDA-3 criteria). Secondary endpoints were, the rate of patients fulfilling the NEDA-3 criteria over the first 12 months of treatment, the rate of patients reaching NEDA-3 over the second year of treatment, the rate of patients free from clinical disease activity (no disability worsening and no relapse), relapse free patients, patients free of disability progression, and, patients free of radiological disease activity. The characteristics of patients who interrupted treatment during the study were compared with those of patients still using Fingolimod at 24 months. For all of these criteria, two populations were considered. The per protocol analysis population included patients still receiving Fingolimod at the evaluation dates (12 months and 24 months), while the survival analysis population also included patients who displayed a disease related event (relapse, disability progression) before the cessation of Fingolimod. The occurrence of such an event allowed these patients to be included in the analysis (as non-responders), even if the treatment was stopped at the evaluation date. Events occurring after therapy cessation were not taken into account contrarily to an intention to treat analysis.

ARR was determined over the first 12 months and over the 24 months of the study. Continuous quantitative data were expressed with average standard deviation (SD). Nominal qualitative data were expressed with absolute number and percentage. The relative reduction in the ARR was also obtained for each patient. A statistical difference between the ARR before and after Fingolimod initiation was explored using a Wilcoxon test. A difference in the rate of patients free from relapse before and after therapy initiation was explored using a Mc Nemar test. A p-value of < 0.05 was set for statistical significance.

This study was approved by the local ethic committee. Data collection and analysis was carried out in accordance with the French law on Informatics and Freedoms (edited on the 6th January 1978, amended by the law of the 1st July 1994 and supplemented by an implementing decree on 9 May 1995). An informed consent form was signed by each participant to enable data entry into the EDMUS database and their use. During the analysis, the data was anonymized.

3. Results

3.1. Population

Between 2012 and 2015, 52 patients with a relapsing-remitting form of MS (RRMS) started treatment with Fingolimod in the FWI. One patient was lost for follow-up visits. Forty-three and 40 patients were still receiving treatment at 12 months and 24 months of follow-up, respectively. Only one participant did not perform his follow-up MRI at 24 months (Fig. 1). Table 1 shows demographic, clinical characteristics and neuroradiological features at baseline. Reasons for Fingolimod initiation are detailed in Fig. 2. Overall, 46 patients had received another treatment prior to Fingolimod initiation with an average of 1.67 treatments (0.80) at study start. Almost 25% of the whole cohort switched to Fingolimod from a highly active second line therapy (Natalizumab or Mitoxantrone). In 40% of participants, Fingolimod was prescribed due to failure of previous therapy (Fig. 2).

3.2. Baseline characteristics of patients who stopped prematurely Fingolimod

Subjects who stopped treatment displayed a more active MS clinically at Fingolimod initiation, with a greater number of relapse reported within the preceding 24 months period ($p = 0{,}049$). Similarly, none of the 11 patients who stopped treatment during the 24 months of follow-up were free of relapse within 12 months prior to initiation of Fingolimod ($p = 0{,}023$). In patients who stopped treatment, MS had a greater duration, with a higher level of disability on EDSS, although no statistically significant differences were observed. In addition, all patients who interrupted treatment during the 24 months of the study received other treatments prior to Fingolimod and > 40% of these same patients switched from Natalizumab or Mitoxantrone therapy.

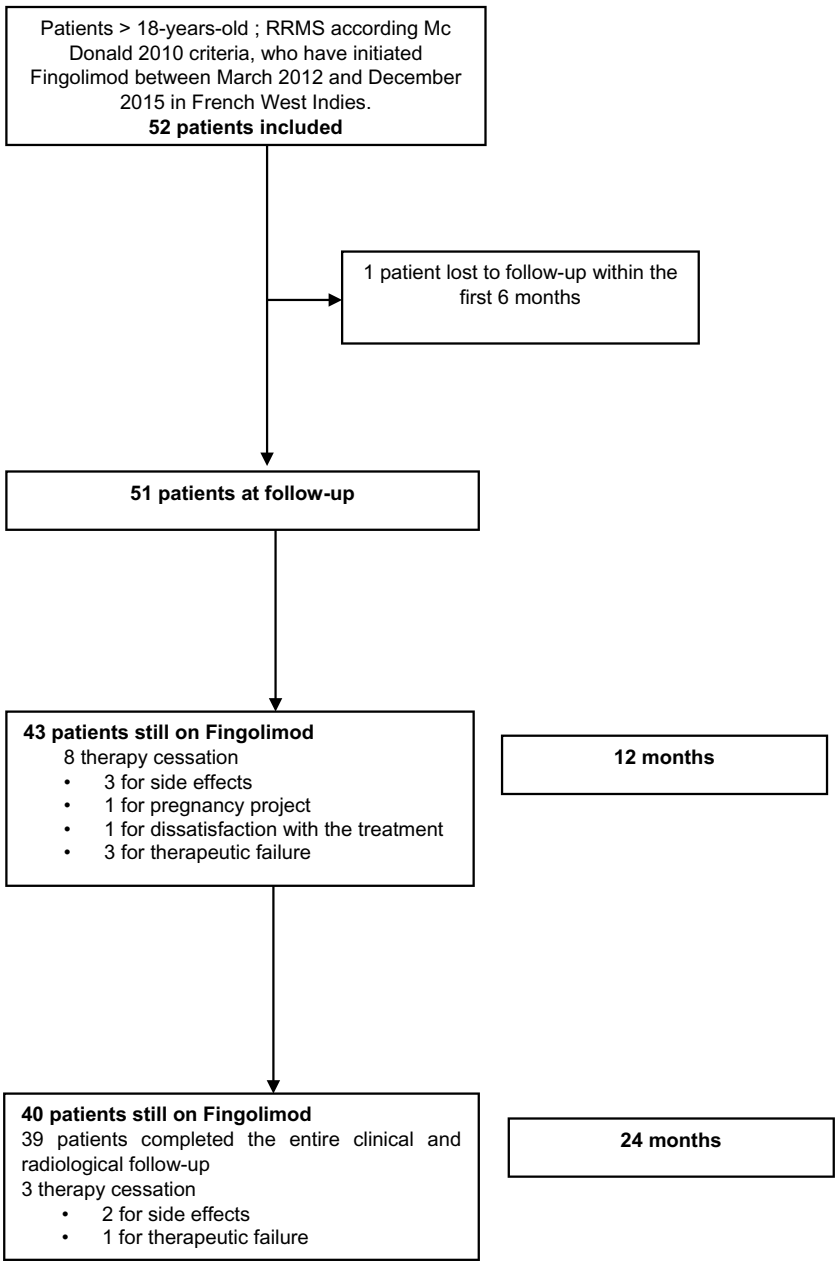

Fig. 1. Flowchart.

3.3. Disease control based on NEDA-3 criteria

The NEDA-3 criteria were fulfilled by 46.51% of patients still treated with Fingolimod at 12 months and 41.03% of the 39 patients still under treatment at 24 months (Fig. 3). Of the 51 patients for whom follow-up was conducted after initiation of Fingolimod, 48 were included in the survival analysis over the 24 months of study. At 12 months, 41.67% of them met the criteria for NEDA-3, while about one third of those still met these criteria over the 24 months period (Fig. 3). For both types of analysis, a larger percentage of patients reached NEDA-3 in the second year of the study (56.41% of the 39 patients considered for per protocol analysis and 53.66% of the 41 patients included in the survival analysis).

Among patients who did not reach NEDA-3 in the first 12 months, six (31.6% of 19 patients in per protocol analysis and 28.6% of 21 patients included in the survival analysis) had a controlled disease in the second year of the study. Conversely, four patients who were controlled over the first 12 months (20% of the 20 patients reaching NEDA-3) did not retain this status over the second year of the study.

3.4. Relapses

The average ARR dropped from 1.00 (0.89) over the 12 months preceding the start of the study to 0.28 (0.55) at month 12 and 0.19 (0.39) at month 24 with Fingolimod therapy (Appendix Table 1), corresponding to a reduction in average ARR of 81% at month 24 ($p < .001$). The first relapse occurred on average 8.6 months (10.4) after Fingolimod initiation, and in 80% of cases it appeared within the first six months. Nearly 75% of patients were free of relapse during the first year, while, during the second year, among patients that remained on therapy, 92.5% were free of relapse (Fig. 4). Out of the 41 to 46 patients included in survival analysis, approximately 70% and 90% were free of relapse over the first 12 months and during the second year of study, respectively (Appendix Table 1).

Table 1
Population characteristics.

N° of patient	52
Age at Fingolimod initiation (years)[a]	41.29 (11.81)
Female: N (%)	37 (71.15%)
History of stay in metropolitan France: N (%)	32 (61.54%)
African descent: N (%)	50 (96.15%)
Age at MS onset (years)[a]	30.67 (9.87)
Mean disease duration (years)[a]	11.04 (8.48)
ARR over the 2 years prior Fingolimod[a]	0.75 (0.61)
ARR over the year prior Fingolimod[a]	1.00 (0.89)
Patient free from relapse over the year prior Fingolimod: N (%)	13 (26.92%)
Baseline EDSS[a]/[b]	3.85 (1.63)/4
High baseline EDSS (> 3.5): N (%)	25 (48.08%)
High lesion burden at baseline on T2-weighted MRI (> 9 lesions): N (%)	42 (80.77%)
Presence of active lesion (gadolinium enhanced) on baseline: N (%)	17 (32.69%)
Switch from highly active MS therapy[c]: N (%)	12 (23.08%)
Fingolimod prescribed de novo: N (%)	7 (13.46%)
Failure of prior treatment: N (%)	22 (42.31%)

MS: multiple sclerosis. ARR: annualized relapse rate. EDSS: Expanded Disability Status Scale.
[a] Mean (standard deviation).
[b] Median value.
[c] Natalizumab or Mitoxantrone.

3.5. Disability

On average, EDSS remained stable from 3.85 (1.63) at the study start to 3.74 (1.96) at month 12 and 3.80 (2.29) at month 24. More than 80% of patients did not display any disability progression in the first year of treatment. Similarly to relapses, disability progression was better controlled during the second year on therapy with 85% of the participants free from disability progression over this period. More than 78% of the 46 patients included in the survival analysis during the first 12 months and nearly 83.3% of the 41 patients included in the survival analysis the second year of the study were free from disability progression (Appendix Table 1).

A total of 65% of patients and 80% of patients showed no clinical signs of MS activity during the first year and during the second year of Fingolimod therapy respectively (Table 2). Over the 24 months of the study, about a half (51.06%) of the 47 patients considered for the survival analysis were free from clinical activity (Table 2).

3.6. Radiological outcome

At month 12, of the 43 patients still under Fingolimod therapy, an increase MRI lesion burden (occurrence of at least one new lesion on T2 weighted MRI) occurred in nine patients (20.9%), while at least one new gadolinium enhanced lesion appeared in four patients (9.3%). In the second year, of the 39 participants that completed the entire follow up, 12 participants (30.8%) presented with at least one new lesion on T2 weighted MRI, and three patients (7.7%) displayed at least one active lesion (gadolinium enhanced). Radiological activity was more frequently observed in the second year, with 66.7% of subjects free from radiological activity over year 2 vs 74.4% in the first year (Table 2).

The main clinical and radiological outcomes at 24 months are represented in Fig. 5.

3.7. Treatment adhesion, retention and tolerance

Of the 51 patients who participated in the study, eleven stopped treatment during the 24-month follow-up period, including eight in the first 12 months (Table 3). The main reason for treatment cessation was side effects (9.8%) followed by therapeutic failure (7.8%), and patient's preference (3.9%). The reasons for treatment cessation are detailed in Table 3.

Nine of the 51 (17.6%) patients who were followed presented with at least one side effect. Four patients had cardiovascular effects at initiation: two patients with bradycardia requiring extended monitoring, one patient showed an acute blood pressure raise, and a para-nodal tachycardia was observed in a single patient. The treatment could be kept for each of these patients.

No serious infection, especially no case of PML, was identified during the observation period, while our population included five

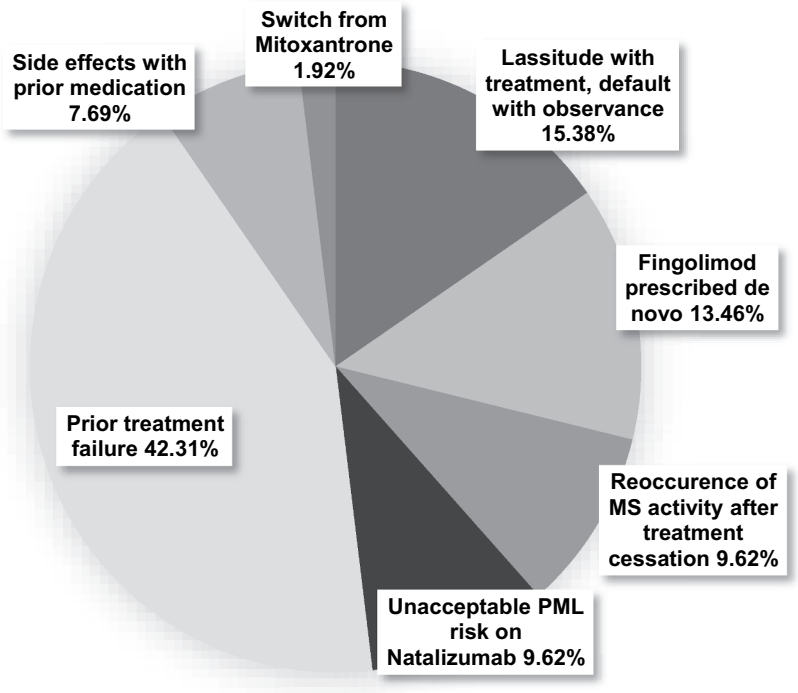

Fig. 2. Reason for Fingolimod initiation.

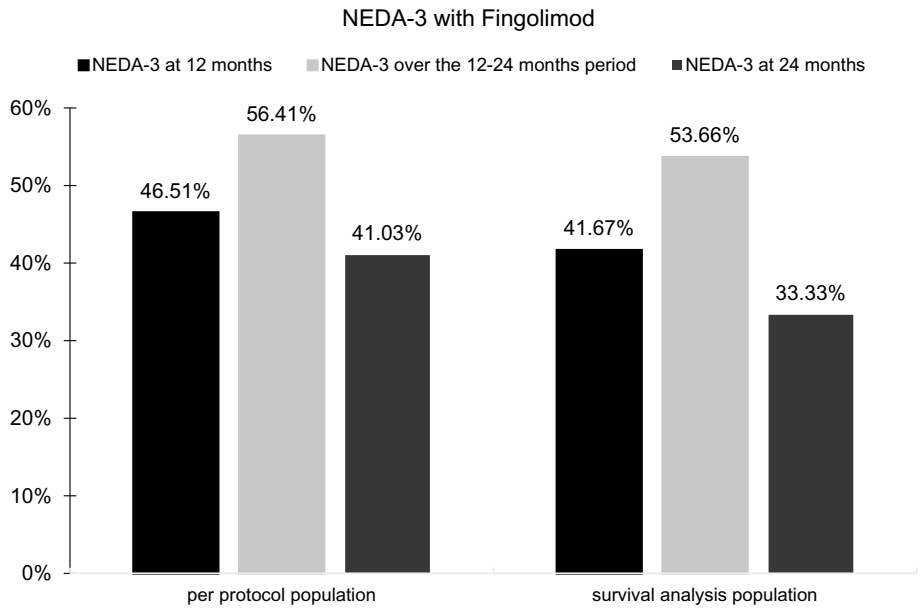

Fig. 3. Proportion of patients who display controlled disease with Fingolimod (according to NEDA-3 criteria). NEDA-3: three criteria No Evidence of Disease Activity (no relapse, no disability progression, absence of new radiological lesion on MRI (T2 weighted and gadolinium enhanced sequences)).

patients who stopped Natalizumab due to a high risk of PML. No pregnancy occurred under treatment during the 24 months of the study.

3.8. Patient switching from Natalizumab or Mitoxantrone

Out of the five patients that started Fingolimod in relay to Natalizumab because of PML risk, four completed the study, with an average ARR of 0.6 (0.58) at year 1 and 0.38 (0.48) over the study period (average ARR at baseline 0.5 (0.58)). Importantly, both relapses that occurred during the first year occurred early after Fingolimod initiation (respectively at month one and month two). While early disability progression was observed in two patients during the first year (from month six), no disability progression was noted during the second year. Overall, no patient met the NEDA-3 criteria over the first year, nor over the 24 months, and only one patient reached NEDA-3 over year 2. The remaining patient stopped the treatment prematurely after 6 months due to early therapeutic failure.

Additionally, one patient started Fingolimod after he completed his treatment with Mitoxantrone. This patient, who was free from relapse the year prior to study commencement, experienced one relapse during year 1 (at seven months). Besides this, he displayed disability progression during year 2 as well as persistent radiological activity (with new lesion and gadolinium enhancement) on both follow-up MRI.

Six patients switched from Natalizumab due to therapeutic failure. Only two of these patients remained on Fingolimod beyond year 1 and completed the study (two patients stopped due to side effects, one for therapeutic failure and one for side effect and therapeutic failure). Before treatment cessation, relapse occurred in two patients, while

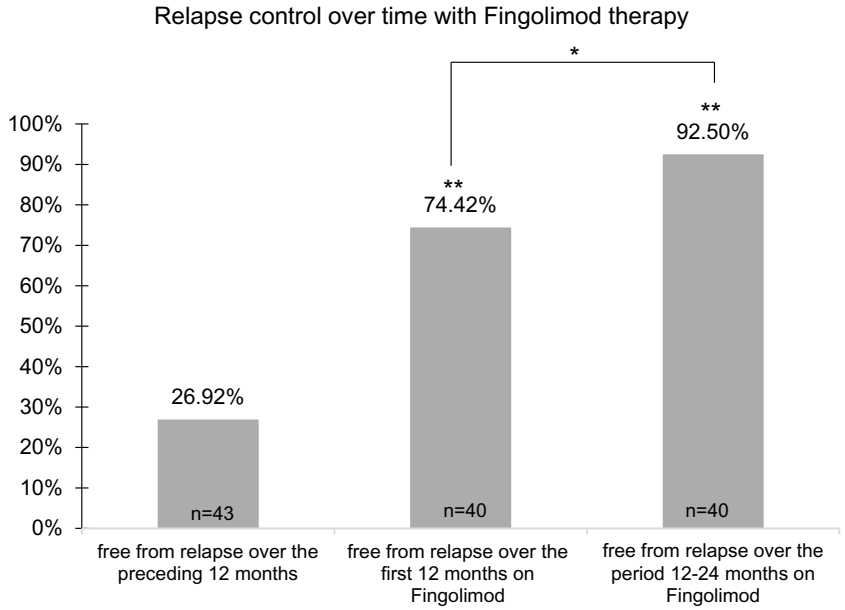

Fig. 4. Percentage of patient free from relapse with Fingolimod. N = number of patient included in the analysis. *p < 0,05, [b]p < 0,01 (comparison with the 12 months prior Fingolimod initiation using a Mc Nemar test).

Table 2
Fingolimod efficacy on disease activity parameters using per protocol and survival analysis. N = number of patients included for analysis. NEDA-3: three criteria No Evidence of Disease Activity (no relapse, no disability progression, no new radiological lesion on MRI using T2 weight sequence and Gadolinium enhanced sequences).

Population	Per protocol	Per protocol	Survival analysis	Survival analysis
Free from clinical activity at 12 months	65.12%	N = 43	58.33%	N = 48
Free from clinical activity over the period 12–24 months	80.00%	N = 40	78.05%	N = 41
Free from clinical activity at 24 months	61.54%	N = 40	51.06%	N = 47
Free from radiological activity at 12 months	72.09%	N = 43	72.09%	N = 43
Free from radiological activity over the period 12–24 months	66.67%	N = 39	66.67%	N = 39
Free from radiological activity at 24 months	64.10%	N = 39	59.52%	N = 42
NEDA-3 at 12 months	46.51%	N = 43	41.67%	N = 48
NEDA-3 over the period 12–24 months	56.41%	N = 39	53.66%	N = 41
NEDA-3 at 24 months	41.03%	N = 39	33.33%	N = 48

Fig. 5. Main outcome at 24 months.

disability progression was observed in a third patient. One patient that completed the study became disease free during year 2.

4. Discussions

To our knowledge, this study is the first to assess, in real-life setting, MS activity with Fingolimod, using the NEDA-3 criteria in AC patients, while these patients are often underrepresented in European studies. Our study supports the efficacy of Fingolimod, to reduce disease activity, relapses, disability progression, and radiological activity. Over the 24 months of study, 33% to 41% of patients didn't show any sign of MS activity based on NEDA-3 criteria, with a clear improvement in MS activity from year 1 to year 2 with Fingolimod therapy.

This improvement, observed between year 1 and year 2, could result from several factors, including early reoccurrence of disease activity after Fingolimod initiation. Thus, during the first months following treatment initiation, disease activity might return, as previous therapy is stopped and Fingolimod is not fully effective yet, especially when a wash-out period is required before starting Fingolimod, as for patients previously treated with Natalizumab. These findings suggest that early

Table 3
reasons for treatment interruption during the study.

Reason for Fingolimod cessation during the first year	N (%)
Total	8 (15.4%)
Side effects:	3 (5.9%)
▪ Macular oedema	1 (2%)
▪ Lower limb erysipela	1 (2%)
▪ Persistant asthenia	1 (2%)
Therapeutic failure/conversion to secondary progressive MS	3 (5.9%)
Patient preference	2 (3.9%)
▪ Pregnancy planning	1 (2%)
▪ Default to adhere to treatment	1 (2%)

Reason for Fingolimod cessation during the second year	N (%)
Total	3 (5.9%)
Side effect:	2 (3.9%)
▪ Lymphopenia	1 (2%)
▪ Steatohepatitis	1 (2%)
Therapeutic failure/conversion to secondary progressive MS	1 (2%)

disease outbreak might not necessarily reflect a therapeutic failure but rather the latency for the treatment to be clinically effective. Thus it may not be appropriate to immediately switch medication if early disease activity is observed after Fingolimod initiation. It's important to note, nevertheless, that conversely to clinical activity, radiological activity appeared to increase between year 1 and year 2 and needs to be assessed on a longer period of time to confirm this tendency.

The rate of patient reaching NEDA-3 appears similar to what has been observed in phase III trials. Thus, post-hoc analysis from TRANSFORMS trial showed 46% of the participant to meet the NEDA-3 criteria at 12 months [11], while in FREEDOMS trial, 33% of patients reached this criteria at 24 months [12]. Nevertheless, one must note that the radiological assessment was performed manually by the neurologist and did not use superposition software, which may have increased the accuracy in detecting new or enlarged T2 lesions.

Two recent studies in real world setting found slightly higher rate of disease control (Totaro et al. 41.9% [13] and Izquierdo et al. 46% at 24 months [14] vs 33.3% of NEDA-3 in our study at the same time). Conversely, a recently published study conducted in Switzerland found only 37% of patients meeting the NEDA-3 criteria after 12 months with Fingolimod vs 41.67% in our study at the same time [12].

Such discrepancy may be due to heterogeneity in the method used for radiological assessment, in the statistical method or even in the population included. Thus, in our study, the baseline EDSS was on average 3.8 with ~50% of participants displaying a baseline EDSS above 3.5, while previously mentioned studies report a lower baseline level of disability (3.1 in both Izquierdo et al. and Rasenack et al. studies [12,14], and 2.52 in the Totaro et al. study [13]).

Our findings regarding relapse control appear comparable with the results of the post-hoc analysis conducted on AA patients from the FREEDOMS II study [1]. Thus, the 24-month ARR was 0.26 in the FREEDOMS II study [1] vs 0.19 in our study. However, in the post hoc analysis from PREFERMS study, ARR appeared to be lower (0.13 at 12 months compared to 0.28 in our study) [2]. This difference may reflect some divergence in the population included. Indeed, in the PREFERMS study, adherence to Fingolimod treatment was compared with adherence to first-line injection therapies and therefore included milder form of RRMS (average baseline EDSS 2.2 and average ARR over the previous 12 months 0.6 (0.9)). Moreover, even with IFN beta1, previously reported as ineffective among patients from African descent, the observed ARR for the first year of study was 0.23 [2]. Nevertheless, despite the discrepancy between the two study populations, the retention rate was similar (80.6% at 12 months in PREFERMS versus 78.48% at 24 months in our study) [2]. The use of both per protocol and survival analysis allows us to have a better idea of MS activity with Fingolimod, as per protocol analysis tends to overestimate the success rate, (since patients that withdraw medication for therapeutic failure are not taken in account) while in the survival analysis, patients that have stopped medication prematurely but without disease activity before treatment cessation are excluded for analysis, leading to an over-representation of patients with disease activity.

In absence of NEDA-3 data at baseline or comparative group treated with Natalizumab in our study, we cannot make any definitive conclusion regarding Fingolimod efficacy compared to Natalizumab among AC patients. However, our findings on relapse rate appear similar to what has been previously described in patients of African descent enrolled in AFFIRM and SENTINEL phase III studies data (ARR 0.3 at 24 months vs 0.19 in our study) [15]. Among patients switching from Natalizumab due to high risk of PML and who completed our study, the ARR remained overall steady. Moreover, in spite of early disability progression observed in two patients out of four during the first year, no further disability progression was observed during year 2. The fifth patient who switched from Natalizumab for the same reason had to interrupt Fingolimod after six months due to early therapeutic failure; importantly, his baseline EDSS was high (5.5), with persistent relapse activity with Natalizumab during the year prior Fingolimod initiation.

Further study in AC patients, comparing global disease activity at baseline and with Fingolimod, especially beyond the first year of treatment would bring valuable information.

Brain volume loss, which is used in the NEDA-4 criteria, was not measured; however, brain volume is not routinely assessed in practice, while the use of the NEDA-3 criteria and the manual method performed in our study for radiological screening seem closer to what is typically done in daily clinical practice. In the future, development of new disease activity biomarker such as neurofilament, could allow for a closer assessment of disease activity and for a better reactivity when treatment fails to control the disease [16,17].

The rate of serious side effects was the same between FREEDOMS II and our study (8.3 to 9.8%) [1]. It's worth noting that we did not observe any case of PML, while the study population comprised an important proportion of patient previously treated with Natalizumab, including five patients who stopped this treatment because of a high risk of PML. However, PML can occur after 24 months and longer monitoring under Fingolimod therapy is required to assess this risk, especially for patients previously treated with Natalizumab [18,19]. Additionally, data on disease activity were not considered after treatment cessation, which precludes addressing the question of disease reactivation after Fingolimod cessation.

In AC patients living in FWI, Fingolimod seems to show an effective and safe profile for the treatment of RRMS. Fingolimod could therefore be a major treatment option for MS in a population that displays poor response to IFN beta1 as well as poor tolerance to Glatiramer Acetate while escalation to second line therapy is often necessary due to a more severe course than in Caucasian patients.

Despite a small number of patients, it is important to note that this study included the whole affected population treated with Fingolimod in FWI for the study period. Furthermore, the insular situation of FWI brings a clear advantage for patients follow up. Extended study with comparative group, longer follow-up and including patients who started the medication after 2015 is warranted to confirm the findings from this pilot study. In France, Fingolimod is prescribed as a second line therapy; however, considering the above mentioned restriction with the use of first line injectable therapies, it may be useful in the future to compare directly the efficacy and safety profile of Fingolimod with the more recently available first line oral therapies for the treatment of RRMS.

5. In conclusion

our study conducted on a comprehensive, unselected population brings reassuring real world data concerning Fingolimod efficacy and safety for the treatment of RRMS in AC patients in FWI. The use of Fingolimod in AC patients in FWI appears to bring similar benefits to MS patients as those reported in previous phase III trials, as well as in real world studies conducted in Europe.

Declaration of interests

None.

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Appendix A

Appendix Table 1
Efficacy of Fingolimod using per protocol and survival analysis.

Analysis	Per protocol	Per protocol	Survival analysis	Survival analysis
ARR at 12 months*	0.28 (0.55)	N = 43	0.28 (0.55)	N = 43
ARR at 24 months*	0.19 (0.39)	N = 40	0.19 (0.39)	N = 40
ARR reduction at 12 months	43.02% (65.08)	N = 43	43.02% (65.08)	N = 43
ARR reduction at 24 months	46.25% (57.89)	N = 40	46.25% (57.89)	N = 40
EDSS at 12 months*/**	3.74 (1.96)/4	N = 43	3.83 (1.99)/4	N = 44
EDSS at 24 months*/**	3.80 (2.29)/4	N = 40	3.88 (2.27)/4	N = 42
Free from disability progression at 12 months	81.40%	N = 43	78.26%	N = 46
Free from disability progression over the period 12–24 months	85.00%	N = 40	83.33%	N = 42
Free from disability progression at 24 months	72.50%	N = 40	66.67%	N = 45
Free from relapse at 12 months	74.42%	N = 43	69.57%	N = 46
Free from relapse over the period 12–24 months	92.50%	N = 40	90.24%	N = 41
Free from relapse at 24 months	72.50%	N = 40	65.91%	N = 44
Free from clinical activity at 12 months	65.12%	N = 43	58.33%	N = 48
Free from clinical activity over the period 12–24 months	80.00%	N = 40	78.05%	N = 41
Free from clinical activity at 24 months	61.54%	N = 40	51.06%	N = 47
Free from radiological activity at 12 months	72.09%	N = 43	72.09%	N = 43
Free from radiological activity over the period 12–24 months	66.67%	N = 39	66.67%	N = 39
Free from radiological activity at 24 months	64.10%	N = 39	59.52%	N = 42
NEDA-3 à 12 months	46.51%	N = 43	41.67%	N = 48
NEDA-3 over the period 12–24 months	56.41%	N = 39	53.66%	N = 41
NEDA-3 at 24 months	41.03%	N = 39	33.33%	N = 48

N = number of patient included in the analysis. ARR: Annualized Relapse Rate. EDSS: Expanded Disability Status Scale. NEDA-3: three criteria No Evidence of Disease Activity.

* Mean (standard deviation).

** Median value.

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