

Évolution clinique et radiologique des patients de Bretagne ayant une sclérose en plaque sous fingolimod

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THÈSE D'EXERCICE / UNIVERSITÉ DE RENNES 1
FACULTÉ DE MÉDECINE
sous le sceau de l'Université Européenne de Bretagne

THÈSE EN VUE DU
DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

présentée par

Cécile Malrain

né(e) le 19 Novembre 1986 à Versailles

**Evolution clinique et
radiologique des
patients de Bretagne
ayant une sclérose
en plaque sous
fingolimod**

**Thèse soutenue à Rennes
le 1^{er} avril 2016**

devant le jury composé de :

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INTRODUCTION

Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the central nervous system (CNS) mainly affecting young adults.

The national prevalence in France is 94.7 per 100 000 patients and the incidence is 7.5 per 100 000 [1]. MS is a common cause of handicap with also social consequences [2].

The etiology of MS is still unknown, but some environmental, genetic [3] and immunological factors have been identified.

The diagnosis is based on the principles of dissemination in space and dissemination in time of CNS lesions, including clinical and radiological criteria, defined according to the Mac Donald classification [4] (Table 1), which allows an early diagnosis.

Table 1. Mac Donald criteria 2010

Clinical Presentation	Additional Data Needed for MS Diagnosis
≥2 attacks ^a ; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack ^b	None ^c
≥2 attacks ^a ; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) ^d ; or Await a further clinical attack ^a implicating a different CNS site
1 attack ^a ; objective clinical evidence of ≥2 lesions	Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack ^a
1 attack ^a ; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For DIS: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) ^d ; or Await a second clinical attack ^a implicating a different CNS site; and For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack ^a
Insidious neurological progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria ^d : 1. Evidence for DIS in the brain based on ≥1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions 2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

If the Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is "MS"; if suspicious, but the Criteria are not completely met, the diagnosis is "possible MS"; if another diagnosis arises during the evaluation that better explains the clinical presentation, then the diagnosis is "not MS."

^aAn attack (relapse; exacerbation) is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection. It should be documented by contemporaneous neurological examination, but some historical events with symptoms and evolution characteristic for MS, but for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should, however, consist of multiple episodes occurring over not less than 24 hours. Before a definite diagnosis of MS can be made, at least 1 attack must be corroborated by findings on neurological examination, visual evoked potential response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms.

^bClinical diagnosis based on objective clinical findings for 2 attacks is most secure. Reasonable historical evidence for 1 past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least 1 attack, however, must be supported by objective findings.

^cNo additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these Criteria. If imaging or other tests (for instance, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS, and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation, and objective evidence must be present to support a diagnosis of MS.

^dGadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes.

MS = multiple sclerosis; CNS = central nervous system; MRI = magnetic resonance imaging; DIS = dissemination in space; DIT = dissemination in time; PPMS = primary progressive multiple sclerosis; CSF = cerebrospinal fluid; IgG = immunoglobulin G.

Lesions observed in the CNS of MS patients are characterized by multifocal areas of myelin sheath destruction, oligodendrocyte death, axonal and neuronal damages, and activation of glial cells. The migration of activated T lymphocytes from the periphery into the CNS is a crucial step in the formation of MS lesions, in the CNS, T lymphocytes need to be reactivated.

Fingolimod

Fingolimod (FTY720) is a sphingosine-1-phosphate–receptor modulator that prevents lymphocyte egressing from lymph nodes, by reducing recirculation of auto aggressive lymphocytes to the CNS. Fingolimod can cross the blood brain barrier due to its lipophilic properties, and it is phosphorylated within the CNS. Through the interaction with sphingosine-1-phosphate receptors on neural cells, fingolimod may have neuroprotective or reparative effects.

Fingolimod is the first oral treatment approved for relapsing remitting (RR) MS, introduced from 2011 in France. The efficacy of fingolimod was demonstrated in two phase III clinical trials:

- In the FREEDOMS trial [5], it reduced annualized relapse rate (ARR) by 54% and risk of disability progression by 30% compared to placebo. Percentage brain volume change was significantly lower in fingolimod group.
- In the TRANSFORMS trial [6], compared to IFNB-1a once weekly, fingolimod reduced ARR by 50%, reduced new or enlarged hyperintense lesions on T2-weighted images and gadolinium (Gd) enhancing lesions on T1-weighted images, but it did not reduce the risk of disability progression. IFNB-1a is a well-known treatment, which reduces relapses incidence, disability and lesions accumulation on MRI [7] for patients with a RRMS.

Fingolimod is indicated as single disease modifying therapy in highly active RRMS for the following adult patients' groups:

- patients presenting high disease activity despite treatment with at least one disease modifying therapy: these patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of at least one disease modifying therapy. Patients should have had

at least one relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gd enhancing lesion. A “non-responder” could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

- or patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gd enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

The most common side effects with fingolimod are flu infections, sinusitis, headache, cough, diarrhea, back pain, raised liver enzyme levels, and lymphopenia. The most serious side effects are infections (multifocal leucoencephalopathy has been described), macular oedema and transient atrioventricular block at the start of treatment [8].

Women should avoid becoming pregnant while taking fingolimod and for at least two months after treatment withdrawal.

Efficacy

The efficacy of treatment in MS use following features:

- no new or enlarging T2-weighted lesions;
- no new gadolinium-enhancing lesions;
- no relapses;
- no confirmed worsening of Expanded Disability Status Scale scores (EDSS).

Table 2

Table 2. Expanded disability status scale (EDSS)

Score	Description
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking
4.0	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m
6.0	Requires a walking aid - cane, crutch, etc - to walk about 100m with or without resting
6.5	Requires two walking aids - pair of canes, crutches, etc - to walk about 20m without resting
7.0	Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but can not carry on in standard wheelchair for a full day and may require a motorised wheelchair
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self care functions
9.0	Confined to bed. Can still communicate and eat
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10.0	Death due to MS

MRI criteria have been recently as biomarkers since they are considered to be more sensitive than relapses or disability progression for measuring disease activity.

New Gd-enhancing lesions, even when completely asymptomatic, are associated with significant demyelination and axonal loss and up to 55% of them may become chronic T1 hypointense lesions (“black holes”) indicative of permanent tissue loss [9]. This accumulation of permanent tissue loss, as seen on MRI, has ultimately proven prognostic value for disability progression [10-11-12]. Thus, the occurrence of MRI activity in this setting would justify a treatment switch to prevent future disability.

Study end point

The aim of this study was to review our clinical experience with fingolimod looking at different outcomes including efficacy (relapse, EDSS, MRI) and safety in real world.

MATERIAL AND METHODS :

Study design/Study procedures

Our study is an observational retrospective multicentric review of a prospectively followed cohort.

We included all patients registered in the data base EDMUS affected with RRMS, and who received fingolimod before 31.12.2013.

EDMUS is a multicentric data base in Brittany including several hospitals: university hospital of Rennes, university hospital of Brest, La Cavale blanche, Quimper, Saint Briec, Saint Malo, Lannion, Pontivy.

The files had been consulted to collect EDSS, relapse, MRI evolution and adverse effects until 31.12.2014.

EDSS before treatment was defined as the EDSS at the introduction or during the year before fingolimod introduction if patients were free of relapses between the EDSS and fingolimod introduction.

Disability progression was defined as an increase of ≥ 1 point in EDSS score (or ≥ 0.5 points if EDSS baseline was ≥ 5).

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.

Since patients underwent MRI at different timings, MRI between 2 and 4 months was considered as the MRI at 3 months, MRI between 5 and 7 months: the MRI at 6 months; the MRI between 9 and 15 months: the MRI at 12 months; the MRI between 15 and 21 months: the MRI at 18 months; and the MRI between 21 and 27 months: the MRI at 24 months.

The same process was used for the EDSS evaluation: EDSS between 2 and 4 months was considered as the EDSS at 3 months, EDSS between 5 and 7 months was the EDSS at 6 months, EDSS between 9 and 15 months is EDSS at one year, EDSS

between 15 and 21 months is EDSS at 18 months, and EDSS between 21 and 27 months is EDSS at 24 months.

Statistical analysis

Continuous variables were reported as means, standard deviations while discrete data were reported in contingency tables as absolute and relative frequencies.

Comparisons between matched groups with categorical variables were made using McNemar test.

Comparisons between unmatched groups with categorical variables were made using Fisher exact test.

Comparisons between independent groups for continuous variables were made with Kruskal-Wallis test.

Statistical significance was considered at a p-value of <0.05 .

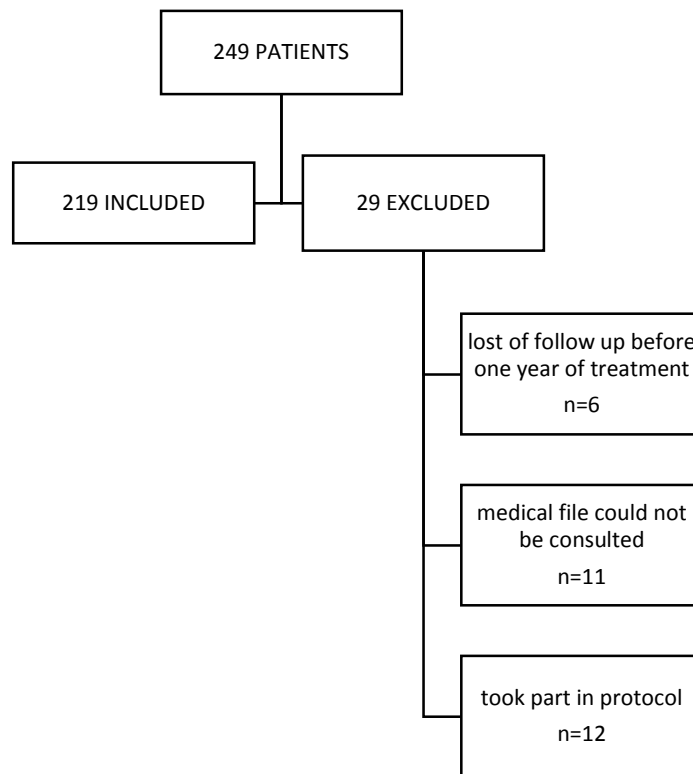
The time taken for a relapse to occur was used to perform survival analysis. Survival rates were calculated by means of the Kaplan–Meier method.

RESULTS

Baseline characteristics

A total of 248 patients were identified from the data base EDMUS. Out of 248 patients, 29 patients were excluded due to lost of follow up during the year after treatment initiation (n=6), inclusion in clinical trials (n=12), missing data because the medical file could not be consulted (n=11). (Figure 1).

Figure 1. Follow chart of the study



Out of the 219 patients included in the study, they had a mean age of 38 +/- 9.4 years and a mean disease duration of 9.6 +/- 6.0 years.

The mean duration of treatment with fingolimod was 1.7 +/- 0.9 years.

Fingolimod was used as first line therapy in 3.2% (n=7) and as second line therapy in 96.8% (n=212). Previous treatment and reason for switching from other treatment are detailed in the table 3.

The annual rate relapse (ARR) was 1 in the previous year, the number of relapses is detailed in the table 5.

32.4% patients (n=71) were relapse free in the previous year.

The mean baseline EDSS was 2.5 +/- 1.8, the number of EDSS by the number of patients is detailed in the table 4.

58.5% patients (n=128) had no Gd enhanced on cerebral MRI, MRI characteristics before fingolimod are detailed in the table 3.

Table 3. Baseline characteristics

Baseline characteristic (n=219)	
Age, mean +/- SD	38,0 +/- 9,4 years
Sexe	male, n= 58 (26,5 %) female, n=161 (73,5%) sex ratio (F/M) 2,8
MS one set, mean +/- SD	28,4 +/- 8,5 years
Disease duration, mean +/- SD	9,6 +/- 6,0 years
Previous treatment	
Previous treatment	teriflunomide, n=1 (0.5%) interferon, n= 69 (31,5%) mycophenolate mofetil, n=2 (0.9%) glatiramere acetate, n=75 (35.4%) mitoxantrone, n=13 (6.1%) cyclophosphamide, n=2 (0.9%) pixantrone, n=1 (0.5%) dimethyle fumarate, n=1 (0.5%) natalizumab, n=47 (22.6%) none, n=7 (3,2%)
Main reason for switching from other DMT to fingolimod	Lack of efficacy, n=115 (52,5%) Poor tolerance, n=40 (18,3%) Programed stop, n=58 (26,5%) JCV seroconversion, n=41 (18,7%) Wish of pregnancy, n=5 (2,3%) Personal wish, n=5 (2,3%)
Duration of previous treatment, mean (+/-SD)	2,1 +/- 2.0 years
Duration between the previous treatment and fingolimod mean +/-SD	0,5 +/- 1,0 years
Relapses	
Number of relapses in the previous year, mean +/-SD (min-max)	1.0 +/- 0.9 (0-5)
Relapse free patients the year before fingolimod	71 (32,4%)
Annual rate relapse (ARR) in the previous year	1
Duration between the last relapse and fingolimod beginning, mean +/- SD	5,1 +/- 4,6 months
EDSS	
Baseline EDSS score, mean \pm SD (min-max) (n=160, 75,47%)	2,5 +/- 1,8 (0-7,5)
MRI	
Time between cerebral MRI and fingolimod begining, mean +/- SD	0,3 +/- 0,3 years
Time between medullar MRI and fingolimod beginning, mean +/- SD	1,1 +/- 2,1 years
Cerebral MRI before fingolimod, n= 211 (96,34%)	Gd+, n= 83 (37,9%) Gd-, n= 128 (58,5%)
Medullar MRI before fingolimod, n= 86 (39,27%)	Gd+, n= 12 (5,5%) Gd-, n= 70 (32.0%)
Patient with out Gd enhanced on cerebral and medullar MRI, n= 81	n=48 (59,3%)
Fingolimod	
Duration of fingolimod therapy, mean +/- SD (min-max)	1,7 +/- 0,9 years
Duration of following since fingolimod beginning, mean +/-SD	2,2 +/- 0,7 years

Table 4. EDSS in the previous year.

EDSS score in the previous year	Patients , n=160
0 - 2,5	n= 99 (61,9%)
3 - 4,5	n= 43 (26,9%)
5 - 6,0	n= 8 (5,0%)
≥6,5	n= 10 (6,3%)

Table 5. Number of relapses in the previous year

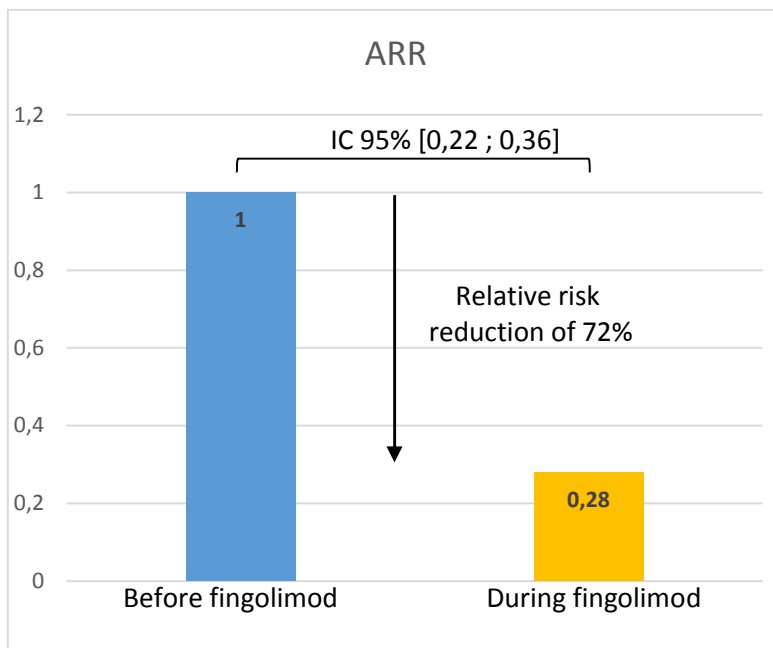
Number of relapses in the previous year	Patients
0	n=71 (32,4%)
1	n=71 (32,4%)
2	n=96 (43,8%)
3	n=40 (18,2%)
4	n=8 (3,6%)
5	n=3 (1,4%)

Efficacy

Relapse

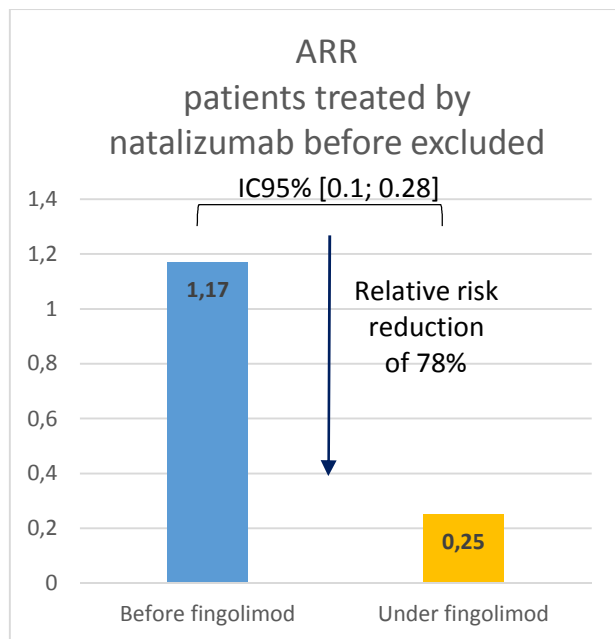
The ARR decreased significantly from 1 the year before fingolimod to 0.28 with fingolimod representing a relative risk reduction of 72% in the ARR, IC95%: [0.22-0.36]. Figure 2.

Figure 2. ARR the year before fingolimod and during fingolimod



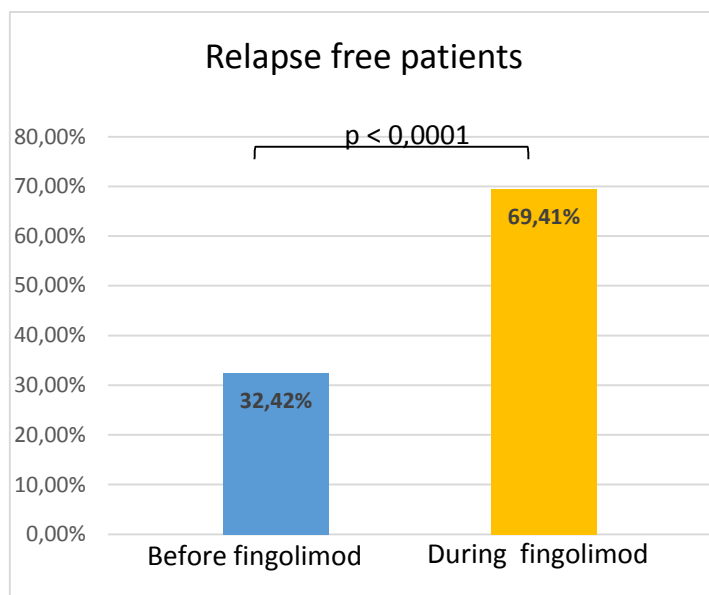
If we exclude patients who were treated by natalizumab before, we have 172 patients, the ARR decreased significantly from 1,17 the year before fingolimod to 0.25 with fingolimod, representing a relative risk reduction of 78% in the ARR, IC95%: [0.1; 0.28]. Figure 3.

Figure 3. ARR the year before fingolimod and during fingolimod (patients treated by natalizumab before excluded)



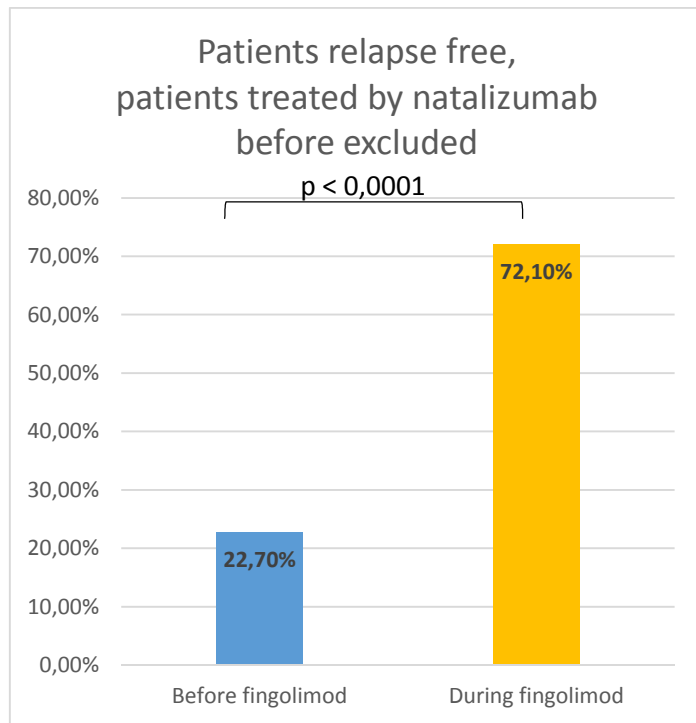
We have a significant increase of the proportion of patients remaining relapse free post-treatment at 69.41% compared to 32.42% the year before fingolimod initiation ($p < 0.0001$). Figure 4.

Figure 4. Relapse free before and after fingolimod



If we exclude patients who were treated by natalizumab before, we have a significant difference between the 22.7% relapse free the year before fingolimod and the 72.1% who are relapse free with fingolimod ($p < 0.0001$). Figure 5.

Figure 5. Relapse before and during fingolimod, patients who were treated by natalizumab before excluded.



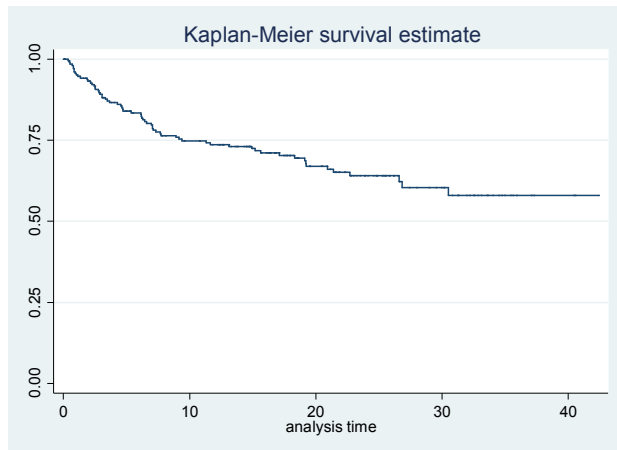
The number of relapse with fingolimod therapy is detailed in the table 6.

Table 6. Number of relapses.

Number of relapse	Number of patients
0	n=152 (69,4%)
1	n=39 (17,8%)
2	n=21 (9,6%)
3	n=5 (2,3%)
4	n=1 (0,5%)
7	n=1 (0,5%)

The mean time from initiation of fingolimod therapy to onset relapse was 0.7 +/- 0.6 years. The duration between the first relapse and fingolimod initiation is represented on the figure 6.

Figure 6. Kaplan-Meier survival estimate for relapse.



The mean time from initiation of fingolimod and other relapse is described in table 7.

Table 7. Mean time for relapse.

Relapse	Time from initiation of fingolimod therapy, mean +/-SD years
1	0,7 +/- 0,6
2	1,3 +/- 0,8
3	1,7 +/- 0,7
4	1,3 +/- 0,5
5	1,2
6	1,7
7	1,9

EDSS, disability

The proportion of patients remaining free of disability progression was 85% at 3 months, 82.4% at 6 months, 86.8% at 12 months, 82.8% at 18 months, 84.4% at 24 months. Table 8.

Table 8. EDSS evolution.

Follow up	Number of patients	Improvement	Stability	Worsening
M3	53	7 (13,2%)	38 (71,7%)	8 (15,1%)
M6	34	6 (17,7%)	22 (64,7%)	6 (17,7%)
M12	83	15 (18,1%)	57 (68,7%)	11 (13,3%)
M18	58	6(10,3%)	42 (72,4%)	10 (17,2%)
M24	32	6 (18,8%)	21 (65,6%)	5 (15,6%)

There is no significant difference on the EDSS during the follow up at 3, 6, 12, 18, 24 months compared to the baseline EDSS score. Table 9.

Table 9. EDSS during fingolimod therapy compared to EDSS baseline.

Following	Number of patients	M0	Follow up	p
M3	53	2,1 +/- 1,9	2,1 +/- 1,8	0,93
M6	34	1,9 +/- 1,6	2,1 +/- 1,5	0,42
M12	83	2,0 +/- 1,6	2,0 +/- 1,7	0,64
M18	58	2,6 +/- 2,0	2,5 +/- 2,1	0,73
M24	32	2,5 +/- 1,9	2,5 +/- 2,1	0,86

MRI outcome

Patients have in mean 1.2 +/- 1.1 MRI during the treatment with fingolimod, 0.7 MRI per year.

60.9% (n=14) patients are free from MRI activity at M6, 71.2% (n=52) at M12, and 81.5% (n=22) at M24.

We have a significant decrease for Gd enhancement at M12 and M24 compared to Gd enhancement at M0.

Table 10. MRI outcome

	Number of patients with a follow up MRI and a MRI before fingolimod	No new lesion compared to M0 MRI	Follow up Gd-	M0 Gd-	p Gd- (follow up-M0)	No new lesion and Gd-
M6	23	15 (65,2%)	17 (73,9%)	12 (52,2%)	0,182	14 (60,9%)
M12	73	53 (72,6%)	60 (82,2%)	47 (64,4%)	0,03	52 (71,2%)
M24	27	21 (77,8%)	23 (85,2%)	15 (53,6%)	0,01	22 (81,5%)

Disease activity

Out of 24 patients in whom relapse rate and MRI outcomes were measured at M6, 11 patients (45.8%) had no disease activity.

Out of 75 patients in whom relapse rate and MRI outcomes were measured at M12, 35 patients (46.7%) had no disease activity.

Out of 27 patients in whom relapse rate and MRI outcomes were measured at M24, 15 patients (55.6%) had no disease activity.

Table 11. Patients relapse free and MRI activity free

Relapse free and MRI activity free	Number of patients
M6, n=24	11 (45,8%)
M12, n=75	35 (46,7%)
M24, n=27	15 (55,6%)

Adverse effects and reasons of interruption

Fingolimod therapy was discontinued in 30.14% of patients (n=66) due to suboptimal response in 6.8% patients (n=15), poor clinical tolerance in 14.5% patients (n=31), biologic trouble in 4.7% patients (n=10) and wish of pregnancy in 5% patients (n=11).

Table 12.

Table 12. Reason to stop the treatment.

Reason to stop the treatment	n= 66
poor clinical tolerance	31 (47%)
pain	7 (10,6%)
asthenia	7 (10,6%)
diarrhea	5 (7,6%)
depression	5 (7,6%)
infectieux	4 (6%)
<i>ORL</i>	1 (1,5%)
<i>sepsis</i>	1 (1,5%)
<i>cystitis</i>	1 (1,5%)
Dermatologic trouble	4 (6%)
Discomfort	3 (4,5%)
cardiologic trouble	3 (4,5%)
head heach	2 (3%)
insomnia	1 (1,5%)
thrombocytopenic purpura	1 (1,5%)
cancer	2 (3%)
others	4 (6%)
biologic trouble	10 (15,2%)
lymphopenia	4 (6%)
hepatic trouble	6 (9%)
wish of pregnancy	11 (16,7%)
inefficacy	15 (22,7%)

48% of patients (n=104) met adverse events with fingolimod therapy.

Lymphopenia defined as lymphocyte count inferior to $200 \times 10^6/L$, occurred in 3.2% patients (n=7) of patients, requiring discontinuation in 4 of them (one of them had still lymphopenia with fingolimod every two days) and decrease of the dose in other 3 patients.

13.7% patients (n=30) had infections, 1.8% of them (n=4) stopped the treatment for this reason.

Three patients presented a cancer during the treatment, 2 of them stopped the treatment for this reason, one had an epidermoide carcinoma, and the other had a melanoma. The two cancer described in the patient who continue the treatment are two cutaneous neoplasia in the same patiente: one melanoma, and one basocellular carcinoma.

Two patients started a pregnancy before two months of fingolimod discontinuation: one of them had a precoce miscarriage, and the other had a normal pregnancy.

3.2% of patients (n=7) had cardiologic troubles, 3 of them had to stop the treatment, two of them the day of introduction because of one atrio-ventricular block, and the other for severe bradycardia requiring isuprel, the third stopped the treatment one day after the introduction because of a persistant bradycardia.

The other patient with cardiologic trouble who follow the treatment had palpitations, one of them had an autentified cardiac arythmia.

The patiente with thrombocytopenic purpura had already this pathology before the treatment, but she had a relapse of her thrombopenia with the fingolimod.

The patiente who had a stroke had a retina ischemia.

None of the patients developed macular edema or multifocal leukoencephalopathy.

2.7% patients (n=6) developed a progressive form under fingolimod.

Table 13. Adverse events

Adverse events	Patients, n= 219	Reason to stop fingolimod	Adverse event continuing fingolimod
poor clinical tolerance	87 (40,7%)	31 (14,15%)	80 (36,5%)
infectieux	30 (13,7%)	4 (1,8%)	26 (11,9%)
<i>ORL</i>	5 (2,3%)	1 (0,5%)	4 (1,8%)
<i>pyelonephritis</i>	3 (1,4%)		3 (1,4%)
<i>abscess</i>	2 (1%)		2 (1%)
<i>bronchitis</i>	2 (1%)		2 (1%)
<i>clostridium difficile colitis</i>	1 (0,5%)		2 (1%)
<i>herpes virus infection</i>	7 (3,2%)		7 (3,2%)
<i>prostatitis</i>	1 (0,5%)		1 (0,5%)
<i>sepsis</i>	2 (1%)	1 (0,5%)	1 (0,5%)
<i>vaginal yeast infection</i>	2 (1%)		2 (1%)
<i>cystitis</i>	2 (1%)	1 (0,5%)	1 (0,5%)
<i>zona</i>	2 (1%)		2 (1%)
pain	19 (8,7%)	7 (3,2%)	12 (5,5%)
asthenia	17 (7,8%)	7 (3,2%)	10 (4,6%)
depression	17 (7,8%)	5 (2,3%)	12 (5,5%)
head heach	10 (4,6%)	2 (1%)	8 (3,7%)
dermatologic trouble	10 (4,6%)	4 (1,8%)	6 (2,7%)
diarrhea	8 (3,7%)	5 (2,3%)	3 (1,4%)
cardiologic trouble	7 (3,2%)	3 (1,4%)	4 (1,8%)
discomfort	7 (3,2%)	3 (1,4%)	4 (1,8%)
cancer	4 (1,8%)	2 (1%)	2 (1%)
nausea	2 (1%)		2 (1%)
cough	2 (1%)		2 (1%)
insomnia	2 (1%)	1 (0,5%)	1 (0,5%)
thrombocytopenic purpura	1 (0,5%)	1 (0,5%)	
stroke	1 (0,5%)		1 (0,5%)
phlebitis	1 (0,5%)		1 (0,5%)
others	10 (5%)	3 (1,4%)	7 (3,2%)
biologic trouble	30 (13,7%)	10 (4,6%)	20 (9,1%)
lymphopenia	7 (3,2%)	4 (1,8%)	3 (1,4%)
hepatic trouble	20 (9,1%)	6 (2,7%)	14 (6,4%)
<i>cytolysis</i>		6 (2,7%)	1 (0,05%)
<i>cholestasis</i>			13 (5,9%)
thrombopenia	1 (0,5%)		1(0,5%)
neutropenia	1 (0,5%)		1 (0,5%)
hypereosino	1 (0,5%)		1 (0,5%)
pregnancy	2 (1%)		2 (1%)

Sub-groups analyses

Switch from natalizumab to fingolimod

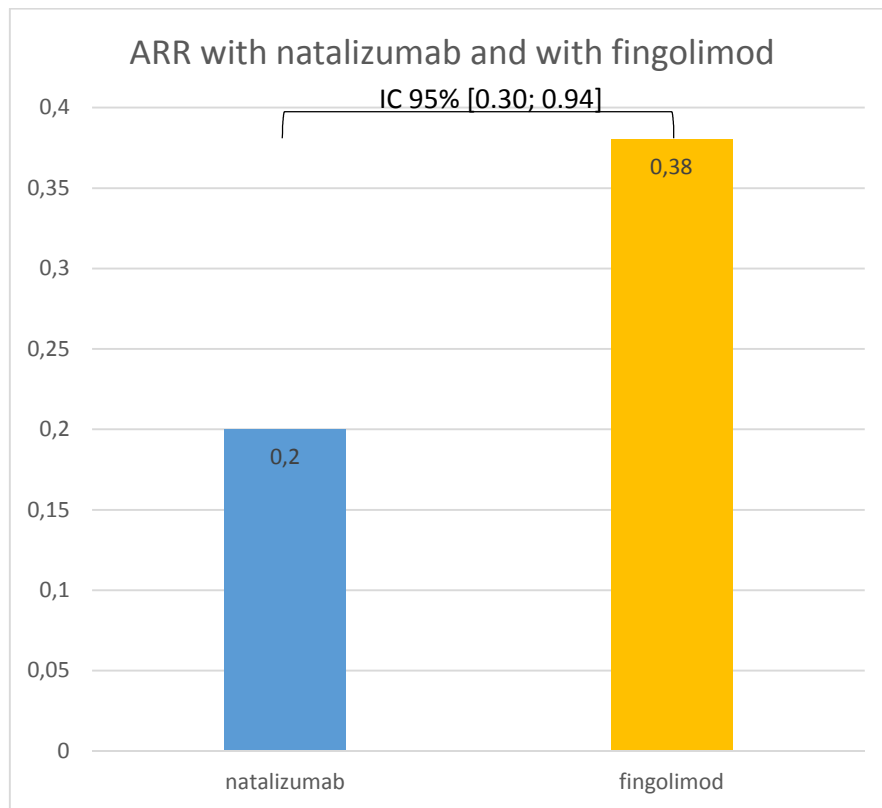
21.9% of patients (n=47) had natalizumab as previous treatment, their characteristic before fingolimod are detailed in the table 14.

Table 14. Baseline characteristics for patients who stopped natalizumab for fingolimod

Previous treatment by natalizumab	n= 47
Reason of switch	
JCV conversion	n=41 (85,4%)
Inefficacy	n=1 (2,0%)
Intolerance	n=3(6,0%)
Convenience	n=2 (4,0%)
Duration of natalizumab, mean +/- SD	2,0 +/- 1,2 years
Wash out period, mean +/- SD	0,3 +/- 0,4 years
Number of patients with a wash out period inferior to 3 months	23 (48.9%)
Number of relapse the year before fingolimod, mean +/- SD	0,4 +/- 0,6
Relapse free the previous year	33 (68,8%)
AAR the year before fingolimod	0,4
ARR with natalizumab	0,2
EDSS before fingolimod, mean +/- SD	2,7 +/- 2,0
Duration of fingolimod, mean +/- SD	1,7 +/- 1,0 years

There is a significant difference between the ARR with natalizumab at 0.2 and the ARR with fingolimod at 0.38, IC 95% [0.30; 0.94]. Figure 7.

Figure 7. ARR with natalizumab and with fingolimod



And we have a significant difference between the ARR with natalizumab at 0.2 and the ARR after natalizumab stop and during fingolimod at 0.4, IC 95% [1.13; 3.41].

The mean time for the first relapse after natalizumab stop is 11.1 months. 5 patients (10.6%) presented a relapse during the wash out period, they all had a wash out period superior to 3 months. Only one patient had a relapse before 3 months, and he presented his relapse before one month, so before the rebound period with natalizumab. The others patients who had relapsed during the wash out period presented their relapse after 3 months.

23 patients (48.9%) had a wash out period inferior to 3 months, those patients had no relapse during the wash out period.

We have no significant difference between the ARR after natalizumab stop for patients with a wash out period inferior to 3 months (0.32) and the ARR after natalizumab for patients with a wash out period superior to 3 months (0.42), IC 95% [0.39; 1.55].

There is no significant difference for the EDSS during the follow up with fingolimod compared to EDSS baseline with natalizumab. Table 15.

Table 15. EDSS during fingolimod therapy compared with EDSS at M0

Follow up	Number of patients	M0	Follow up	p
M3	10	2,2 +/- 2,2	2,5 +/- 2,1	0,33
M6	9	1,9 +/-1,2	2,3 +/- 1,7	0,46
M12	17	2,0 +/- 1,1	2,1 +/- 1,4	0,53
M18	14	2,9 +/- 2,1	3,1 +/- 2,3	0,27
M24	7	2,0 +/- 2,8	2,1 +/- 2,7	0,88

Patients who stopped fingolimod for inefficacy

6.9% patients (n=15) stopped fingolimod because of inefficacy, they had fingolimod during 1.4 +/- 1.0 year.

33.3% patients (n=5) were relapse free before fingolimod, and 13.3% patients (n=2) were relapse free with fingolimod, there is no significant difference (p=0.37).

The ARR before fingolimod was 0.93, and the ARR with fingolimod is 1.07, there is no significant difference IC95% [0.08 ; 14.15].

The first relapse appeared at 7.1 +/- 8.3 months.

There is no significant difference between EDSS before fingolimod and EDSS during the treatment for people who stopped fingolimod for inefficacy. Table 16.

Table 16. EDSS evolution compared to EDSS baseline for patients who stopped fingolimod for inefficacy.

	Number of patients	EDSS M0	Follow EDSS	IC95% EDSS M0-following EDSS
M3	2	2,6 +/- 0,3	2,3 +/- 0,3	0
M6	6	1,8 +/-0,2	2,3 +/- 0,2	[-1,26 ; 0,42]
M12	5	2,4 +/- 0,3	2,4 +/- 0,3	[-0,44 ; 0,44]
M18	3	2,8 +/- 0,6	3,1 +/- 0,6	[-1,77 ; 1,1]

There is no significant difference between patients who stopped the treatment for inefficacy and others patients on gender, age, age of MS one set, disease duration, gadolinium enhancement before fingolimod, EDSS baseline, relapse free before fingolimod, ARR before and with fingolimod, table 17.

Table 17. Characteristics of patients who stopped fingolimod for inefficacy compared to the others patients.

	Stop for inefficacy, n=15	Others patients, n=204	Significance
Sexe, female	14 (93,3%)	147 (72,1%)	p=0,125
Age	34,5 +/- 9,9	38,3 +/- 9,3	p=0,137
MS onset	25,6 +/- 10,2	28,6 +/- 8,4	p=0,188
Disease duration	8,9 +/- 6,1	9,7 +/- 4,9	p=0,649
Cerebral Gd+ before fingolimod	7 (46,7%)	76 (38,8%)	p=0,590
Medullar Gd+ before fingolimod	1 (10,0%)	11 (15,3%)	p=1
Baseline EDSS	2,7 +/- 1,3	2,5 +/- 1,9	p=0,7
Relapse free before fingolimod	5 (33,3%)	66 (32,4%)	p=1
ARR before fingolimod	0,9	1	IC95% [0,06 ; 18,1]
ARR with fingolimod	1,1	0,2	IC95% [0,01 ; 6,88]

Patients who stopped fingolimod for wish of pregnancy

11 patients (16.7%) stopped fingolimod for wish of pregnancy.

They had fingolimod in mean 1.2 +/- 0.7 years, and they stopped the treatment in mean 1.1 +/- 0.4 years.

72.7% of this patient where relapse free with fingolimod, they had a mean EDSS of 1.0 +/- 0.8.

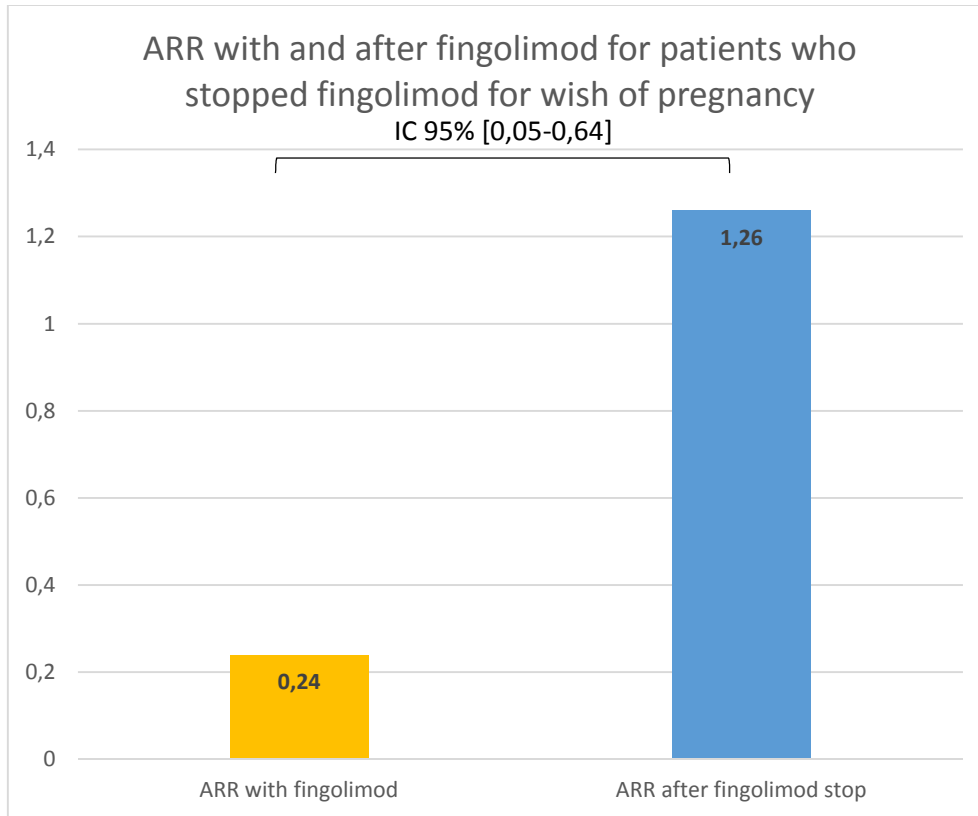
5 of them had a temporary stop of fingolimod, the 6 others had not taken fingolimod at the end of the study.

We have a significant increase of the ARR from 0.40 to 1.26, IC95% [0.05-0.64] after fingolimod stop for patient who stop the treatment for wish of pregnancy. Figure 8.

The mean time to the first relapse is 3.4 +/- 2.8 months.

Only two of them had a relay treatment when fingolimod is stopped: one had copaxone and had no relapse after fingolimod stop. The other had an interferon and had two relapses with this treatment, she had only one relapse with fingolimod. A third one had alemtazumab, 3 months after fingolimod stop because of a serious relapse with an MRI with a lot of Gd enhancement.

Figure 8. ARR with and after fingolimod for patients who had stopped fingolimod for wish of pregnancy.



DISCUSSION :

Our cohort reflects the “real world condition” of fingolimod use during in mean 1.7 +/- 0.9 years in 219 patients. This is important because patients are not exactly the same as in randomized controlled trials and in real clinical practice: patients are of different ages, different disease duration, different disease activity, varying comorbidities, patients can be less invested in their treatment: doses may be omitted.

The main limitation of this cohort study is the retrospective nature of our review, and the lack of EDSS and MRI.

We report here our clinical experience with the use of fingolimod in daily practice in Brittany.

Efficacy

Compared with other studies

The ARR decreased by 72% on fingolimod therapy in our study, which was slightly lower than the relative risk reduction of 88% and 89% observed in the clinical trials FREEDOMS [5] and TRANSFORMS [6], respectively. Other post marketing studies reported a quite similar relative risk reduction for ARR such as: Latin America [13], Lebanese [14] with a ARR reduction of 69% and 75%, respectively.

Some studies published a lower relative risk reduction for ARR as a Portuguese study (51.92%) [15], or a US study reporting a reduced risk of ARR of 59% for patients switching from IFNB to fingolimod [16]. A possible explanation for these differences is the variability of ARR at baseline which was highest in the study who reported the highest relative risk reduction for ARR: 1.5 in FREEDOMS [5] and TRANSFORMS [6], moderate in our cohort (1) and in the Lebanese cohort (1.16) [14], and lowest in the study who find a lower relative risk reduction for ARR (0.46 in the US study) [16].

The proportion of patients relapse free in our cohort is 69.41% comparable with the original trial FREEDOMS [5]: 70.4%, and some observational studies: Lebanese (77.3%) [14], Baldi Italian study (69.30%) [17]. Other studies have a higher rate of patients relapse free: 82.6% in TRANSFORMS [6], 88.10% in Totaro Italia study [18], 86.3% in a study from Kuwait [19], 87.3% in Hersh study [20]. But the proportion relapse free before fingolimod was the same in our study (32%), and in the study from Kuwait.

The proportion of patients free of disability progression in our cohort was 84.37% at 24 months comparable to 82.3% in FREEDOMS trial [5], 80% in Lebanese study [14].

The proportion of patients free of disability progression was lower in Totaro Italian study at 70% [18] and higher in TRANSFORMS trial [6] at 94.1%.

Results are discordant in different study on the significant improvement of EDSS.

We have no significant change in the EDSS with fingolimod as it was described in TRANSFORMS [6] and FREEDOM [5], and in other study: Portuguese one [15], and Italian studies [17-18]. Some study have shown an improvement on the EDSS: the

Lebanese study [14], Mexican study [21], study from Kuwait [19]. This does not seem to be due to the EDSS difference before fingolimod or treatment naïve.

The proportion of patients free from any radiological activity (New T2 or Gd+ lesions) was 84.8% in our cohort and other observational studies (81.%) [22] compared to 50.5 % in FREEDOMS trial [5] and 54.8 % in TRANSFORMS trial [6], 66.3% in Lebanese study [14], 54.9% in Baldi Italian study [17], this is higher but the percentage of patients free from Gd enhancement is similar before treatment around 60% in the different study.

We have not a significance difference at M6 for Gd enhancement, this could be explain, because fingolimod is not yet to its full efficacy.

For disease activity we did not include EDSS evolution, because of data missing.

In real world, patients treatment naïve are very lower 3.2% in our study, 6% in Portuguese study [15], 3.5% in Hersh study [20], 12% in Lebanese study [14], 21% in a study from Kuwait [19], than in clinical trials 57% in FREEDOMS [5] and 45.8% in TRANSFORMS [6].

Compared with others treatments

It seems fingolimod is less effective than natalizumab to prevent relapses, disability progression and new T2 and Gd-enhancing lesions at 1 and 2 years [23 - 24].

Fingolimod therapy results in a higher probability of NEDA than dimethyl fumarate and teriflunomide therapy when phase 3 trial data are indirectly compared and differences between trials are adjusted for [25].

Safety

30.14% patients discontinued treatment permanently, this is higher than in all other studies 7.5% in FREEDOMS [5], 5.6% in TRANSFORMS [6], 1.6% in Lebanese study [14], 10.6% in Portuguese study [15], 9.10% in Totaro Italian study [18], 24.8% in Hersh study [20], maybe patients are less tolerant to clinical adverse effects, because the proportion of patients who stopped for inefficacy or biologic intolerance are the same as in the other study, and we do not have more adverse events.

48% met adverse event in our study, this is quite heterogenous between different studies from 94% in FREEDOMS [5] to 24% in Koweit study [19], sometimes it is difficult to know if the adverse event is really due to fingolimod.

None of our patients developed macular oedema, or multifocal leukoencephalopathy. In our study two patients had to stop the treatment the day of the introduction because of serious bradycardia, this should encourage us to be careful with cardiologic follow. Infections occurred in 13.7% of our patients and were mostly mild to moderate. The rate of infections was much higher in both the FREEDOMS [5] and TRANSFORMS [6] trials, but this is probably related to the strict adverse event reporting in clinical trial study.

These data will be assess by the French national data base VIRGIL.

Due to its safety and efficacy fingolimod had an extension of indication in second line use to 'patients with active disease defined by clinical or imaging features despite treatment with at least one disease modifying therapy'.

Sub groups

Switch natalizumab to fingolimod

One French study find 27% patients relapsed during the wash out period [26], in our study only 10.6% relapsed during the wash out period, maybe due to the wash out period which is a little shorter in our study (14 weeks versus 17 weeks). This same French study has shown that a wash out period shorter than 3 months was associated with a lower risk of relapse but in our study we have no significant difference between the ARR after natalizumab stop for patients with wash out period inferior to 3 months compared to those with a wash out period superior to 3 months, but we have no relapse during the wash out period for patients with a wash out period shorter than 3 months. In our study, we have a significant increase of the ARR with fingolimod compared with natalizumab, as shown in an other study [27], maybe fingolimod is not the ideal relay treatment after natalizumab stop.

Patients who stop the treatment for wish of pregnancy

We have a significant increase of the ARR after fingolimod stop, this could encourage us to discuss a relay treatment after fingolimod stop for wish of pregnancy.

CONCLUSION

In conclusion, our cohort and other post marketing studies confirm the efficacy and safety of fingolimod in the treatment of RRMS in a real world setting, this has been assessed by its extension of indication.

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TITRE DE LA THESE d'EXERCICE

(Ce document sera à insérer dans les thèses définitives)

Titre : Evolution clinique et radiologique des patients de Bretagne ayant une sclérose en plaque sous fingolimod

<p>Rennes, le 16.02 2016</p> <p>Professeur Gilles EDAN <i>Chef du Pôle Neurosciences</i> <i>Service de Neurologie</i> CHU Pontchaillou N° ADEL 35 1 021944</p> <p>Le Directeur de thèse</p>	<p>Rennes, le 17/2/2016</p> <p>Professeur Marc VERIN <i>Chef de service</i> <i>Neurologie</i> CHU de Rennes 2, rue Henri Le Guilloux 35033 RENNES CEDEX</p> <p>Le Président de jury</p>
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Vu et permis d'imprimer

<p>Rennes, le</p> <p>UNIVERSITÉ DE RENNES 1</p>	<p>22 FEV. 2016</p> <p>Le Président de l'Université de Rennes1</p> <p>G. CATHELINÉAU</p>
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MALRAIN Cécile- Evolution clinique et radiologique des patients de Bretagne ayant une sclérose en plaques sous fingolimod

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Résumé

Introduction : Le fingolimod est un traitement de fond des formes très actives de sclérose en plaque rémittente-récurrente (SEP RR) commercialisé en France depuis 2011. C'est est un immunosuppresseur modulateur du récepteur de la sphingosine-1-phosphate permettant de bloquer les lymphocytes en périphérie empêchant leur passage dans le système nerveux central. Le but de notre étude est de voir l'évolution clinique et radiologique des patients de Bretagne ayant une SEP RR sous fingolimod afin d'avoir un reflet de son efficacité et de sa sécurité d'emploi en pratique courante.

Matériel et méthodes : Nous avons inclus tous les patients de Bretagne de la base EDMUS ayant une SEP RR ayant reçu du fingolimod jusqu'au 31.12.2013. Le recueil de données s'est arrêté au 31.12.2014. L'ensemble des dossiers ont été relus afin de collecter les poussées, les EDSS, les IRM, les effets indésirables et les motifs d'arrêt sous fingolimod.

Résultats : Nous avons inclus 219 patients. Sous fingolimod, le taux annuel de poussée (TAP) a diminué de façon significative de 72% de 1 à 0.28, IC95%: [0.22-0.36]. Sous fingolimod, il y avait une augmentation significative à 69.41% du taux de patients ne présentant pas de poussée ($p < 0.0001$). Le délai moyen de survenue de la première poussée était de 0.65 +/- 0.63 mois. Nous n'avons pas constaté de différence significative sur les EDSS de suivi comparés à l'EDSS à l'instauration du traitement. Parmi les patients 84.37% ne présentaient pas de progression du handicap à 2 ans. 60.87% patients n'avaient pas d'activité IRM à six mois, 71.23% à un an, et 81.48% à deux ans. Il y a une diminution significative du taux de patients avec des prises de contraste à M12 ($p=0.03$) et à M24 ($p=0.01$), comparé à l'instauration du traitement. 60.9% des patients n'ont pas d'activité IRM ni poussée à M6, 71.2% à M12 et 81.5% à M24.

Le fingolimod a été arrêté chez 30.14% des patients : 6.8% ont cessé pour inefficacité, 14.5% pour mauvaise tolérance clinique, 4.7% pour intolérance biologique (lymphopénie ou trouble du bilan hépatique), 5% pour désir de grossesse. Des effets indésirables ont été rapportés chez 48% des patients : 13.7% ont présenté des événements infectieux, 3.2% ont présenté des événements cardiaques. Aucun patient n'a présenté d'œdème maculaire ni de leucoencéphalopathie multiple progressive.

Pour les patients précédemment traités par natalizumab, il y a une augmentation significative du TAP sous fingolimod (0.38) comparé au TAP sous natalizumab (0.2) IC 95% [0.3 ; 0.94]. Il n'y a pas de différence significative sur l'EDSS de suivi. Il n'y a pas de différence significative sur le TAP après l'arrêt du natalizumab pour les patients ayant une durée de wash out inférieure à 3 mois et ceux ayant une durée de wash out supérieure à 3 mois.

Les patients ayant arrêté le fingolimod pour inefficacité avaient des caractéristiques initiales similaires aux autres patients (âge, durée d'évolution de la maladie, âge de la première poussée, EDSS, TAP, pourcentage de patients sans poussée) avant la mise sous fingolimod.

Il y a une augmentation significative du TAP de 0.4 à 1.26 IC95% [0.05-0.64], après l'arrêt du fingolimod chez les patientes l'ayant arrêté pour désir de grossesse.

Conclusion : Notre étude ainsi que les autres études suite à la mise sur le marché du fingolimod confirment son efficacité et sa sécurité d'emploi, ce qui va dans le sens de son extension d'indication.

Mots clés : sclérose en plaque, fingolimod

Mots clés anglais MeSH : multiple sclerosis fingolimod