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Reasons for switching to fingolimod in patients relapsing-remitting multiple sclerosis in France: the ESGILE study

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ABSTRACT

Background: Timely treatment switching is an important strategy in optimising management of patients with relapsing remitting multiple sclerosis (RRMS). Patient preferences, as well as clinical benefit, may contribute to the switch decision. Information on reasons determining switching choices and on outcome according to the reason for switching is scarce. Study objectives were to describe the consequences of switching to fingolimod in terms of clinical improvement according to the reasons underlying the switch and to evaluate treatment acceptability from the patient's perspective.

Methods: This prospective observational study was conducted by 71 neurologists in France and included patients with RRMS switching to fingolimod following ≥ 6 months treatment with a first-line disease modifying treatment (DMT). Reasons for switching were documented. Patients were evaluated at inclusion and 12 months after initiating fingolimod. Physicians documented clinical status by relapse activity, disability (EDSS) at each visit and improvement with the Clinical Global Impression – Change (CGI-C) at Month 12. Patients rated improvement at Month 12 with the Patient Global Impression – Change (PGI-C) and treatment acceptability with the ACCEPT[®] questionnaire. Adverse events reported during fingolimod treatment were documented.

Results: Overall 232 patients were recruited of whom 190 could be analysed. Multiple reasons for switching were frequently given; 113 patients (59.4%) switched from a first-line injectable DMT. Switching was motivated by disease worsening in 161 patients (84.7%), tolerability in 35 (18.4%) and patient preference in 58 (30.5%). During the follow-up period, 38 patients (20.0%) experienced at least one exacerbation. The mean EDSS score was stable (2.0 ± 1.3 at inclusion; 2.0 ± 1.5 at M12). With the CGI-C, 67 patients (38.7%) were considered improved and 23 (13.3%) worsened. Although no obvious differences in CGI-C ratings were observed as a function of the reason for switching, when patient preferences entered into the decision, the proportion of patients considered minimally improved was somewhat higher (37.7%) and the proportion considered unchanged somewhat lower (41.5%). With the PGI-C, more patients rated themselves improved than were rated as improved by the physician: of 64 patients rated as 'no change' on the CGI-C, 21 (32.8%) rated themselves as 'improved' and 10 (15.6%) as 'worsened'. The overall level of agreement between the two measures was moderate ($\kappa = 0.48$ [95% CI: 0.35 – 0.60]). The mean general treatment acceptability score on the ACCEPT[®] questionnaire was 42.7 [95%CI: 34.5 – 50.9] at inclusion (reflecting acceptability of the previous DMT) and 64.6 [95%CI: 57.6 – 71.6] at M12 (reflecting acceptability of fingolimod). Mean dimension scores ranged from 36.7 for effectiveness to 72.2 for medication inconvenience at inclusion and from 63.4 for effectiveness to 96.8 for medication inconvenience at M12. The frequency and nature of

reported adverse events was consistent with the well-characterised safety profile of fingolimod.

Conclusion: Most patients switching from a first DMT to fingolimod do so due to persistent disease activity during the initial treatment, although patient preferences are also important. Switching is followed by a reduction in disease activity, perceived improvement in the clinical state of the patient and improved acceptability of treatment.

Keywords: multiple sclerosis, fingolimod, switching, treatment acceptability, patient-reported outcome.

1. Introduction

Over the last decade, the options available for the treatment of relapsing remitting sclerosis (RRMS) have increased considerably, in particular with the introduction of disease modifying treatments (DMTs) that can be administered orally, starting with fingolimod in 2011 (Druart et al., 2018), and the availability of a range of therapeutic monoclonal antibodies.

Since none of the current first-line DMTs can be guaranteed to provide an optimal therapeutic response in all patients with RRMS, switching to an alternative therapy in case of inadequate control of disease activity or poor tolerability is a commonly used management strategy (Hansen et al., 2015; Lebrun-Frenay et al., 2019; Miller, 2016). The availability of a wider range of DMTs provides more opportunities for switching, and this has led to more frequent and earlier switching. Indeed, current practice guidelines from the European Committee of Treatment and Research in Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) recommend that patients starting a DMT should be actively monitored, including with magnetic resonance imaging (MRI) and switched to a more efficacious treatment if clinically or radiologically manifest disease activity persists (Montalban et al., 2018). A recent large (~3000 patients) Italian study reported that 48% of patients switched to a second-line therapy within three years, and that this rate had increased four-fold over the period 2010 – 2017 for switches due to inadequate efficacy and six-fold for those due to tolerability issues (Sacca et al., 2019). In the case of fingolimod, (Bergvall et al., 2014; Cohen et al., 2013; Fox et al., 2014; Freedman et al., 2019) a number of studies have shown improvements in disease control in patients who switch to this drug when disease activity persists under therapy with first-line injectable DMTs (interferon- β or glatiramer acetate).

The reasons for switching may include partial efficacy, tolerability issues and patient-related factors such as lassitude with injections or lifestyle issues. These reasons are likely to differ according to the initial DMT with which the patients were treated and according to the DMT to which they were switched. There is relatively little information on reasons determining switching choices, notably with respect to patient-related factors. For this reason, we have undertaken a study to document the reasons for switching patients from a first-line DMT to fingolimod in everyday clinical practice in France, and to evaluate the extent of improvement from the point of view of the neurologist and of the patient, according to the reasons for choice.

The primary objective of this observational study was to describe the consequences of switching to fingolimod in terms of clinical improvement measured with the Clinical Global Impression (CGI) rating scale after twelve months according to the reasons underlying the switch. Secondary objectives were to evaluate improvement and treatment acceptability

from the patient's perspective and to collect further data on the safety profile of fingolimod in routine clinical practice.

2. Methods

ESGILE was a prospective, multicentre observational study conducted in France. The study was conducted between January 2015 and January 2019 by community or hospital-based neurologists who treated patients with MS.

2.1. Participants

The study was proposed by mail to neurologists identified in a national listing (Onekey; CEGEDIM) covering >95% of all practicing neurologists in France. Each participating physician was expected to invite the next four patients consulting consecutively who fulfilled the eligibility criteria to participate in the study.

Patients diagnosed with relapsing-remitting multiple sclerosis according to the revised (2010) McDonald criteria (Polman et al., 2011) previously treated with a single DMT for at least six months and for whom a switch to fingolimod had been decided were eligible for the study. The decision to switch to fingolimod should have been made independently of participation in the study and fingolimod should have been initiated at the earliest four weeks before the inclusion visit. Patients were required to be aged between 18 and 65 years inclusive, to correspond to the approved indication for fingolimod as a second-line treatment at the time of the study and to have an Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) no higher than 5.5. Patients who had previously received multiple DMTs for over six months each, patients with a progressive form of MS, patients with contraindications to fingolimod and patients unable to understand or complete the study questionnaire were ineligible.

2.2. Study procedures

Since this was an observational study, participation in the study did not affect patient care and there were no protocol-imposed procedures. Physicians were thus free to pursue their treatment and follow-up procedures as they saw fit. Follow-up visits were programmed according to the participating neurologist's normal practice or as needed by the patient's medical state.

During the study, patients were evaluated at an inclusion visit and at two follow-up visits at approximately Month 6 and Month 12. A margin of ± 3 months for these follow-up visits was accepted. Fingolimod was to be initiated at, or at most 35 days before, the inclusion visit. The neurologist completed an electronic case report form (e-CRF) for each patient. At each visit, a physical examination was performed and disability rated with the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). Magnetic resonance imaging data were documented when available. At inclusion, data were recorded on demographics, medical and treatment history, and on the reasons underlying the switch of treatment. These reasons were identified on a pre-specified checklist which was based on unpublished

findings of a previous pilot survey of eighty neurologists in France. At the two follow-up visits, exacerbations since the previous visit were documented, as well as any adverse events occurring in the intervening period, as reported by the patient in response to undirected questions from the physician. The physician completed the Clinical Global Impression – Change questionnaire (CGI-C) (Guy, 1976) at both follow-up visits.

At each visit, the patients was invited to complete a paper questionnaire which included two patient-reported outcome measures (PRO), the ACCEPT[®] questionnaire (Lambert et al., 2018), which was completed at all visits, and the Clinical Global Impression – Change questionnaire (PGI-C) (Guy, 1976), which was only completed at the two follow-up visits.

The CGI-C and PGI-C are identically constructed rating scales on which the clinician (CGI-C) or patient (PGI-C) is invited to rate how much the patient’s illness has evolved since the previous assessment on a seven-point Likert scale ranging from 1 (very much improved) to 7 (very much worse). A rating of 4 indicates no change. ACCEPT[®] is a multidimensional 25-item questionnaire, composed of six dimensions relating to specific treatment attributes (medication inconvenience, long-term treatment, regimen constraints, numerous medications, side-effects and effectiveness) and a general treatment acceptance dimension. It is easily and rapidly completed by the patient and covers relevant and important aspects of the effectiveness and constraints of DMT therapy. The attribute-specific items are presented as multiple-choice questions with three response modalities (*‘Yes and I don’t find this easy to accept’*; *‘Yes and I find this easy to accept’* or *‘No’*). The general dimension consists of three questions (*‘Do you agree with the statement that your treatment has more advantages than disadvantages’*, *‘Taking into account its advantages and disadvantages, does you treatments seem to be an acceptable solution for you?’* and *‘In the long-term, are you convinced that your treatment is worth taking?’*), each scored on a five-point Likert scale. Scores are linearly transformed to range from 0 to 100 for all multi-item dimensions with a higher score indicating greater acceptance. All questionnaires were used in their validated French translations.

2.3. Data analysis

Different study populations were defined. The Included Population included all patients enrolled, the Safety Population included all enrolled patients who had taken at least one dose of fingolimod, the Analysis Population consisted of those members of the Safety Population who fulfilled the eligibility criteria and who attended at least one follow up visit (at M6 or M12) and the Completer population consisted of those members of the Analysis Population for whom the CGI-C had been completed at the inclusion and at both follow-up study visits. The principal analyses were performed on the Analysis Population. The analysis of adverse events was performed in the Safety Population. Adverse events were classified by

System-Organ Class and by Preferred Term using the coding specified in the Medical Dictionary for Regulatory Activities Version 20.0.

The presentation of the data is purely descriptive and no *a priori* hypotheses were tested. Continuous data are presented as mean values \pm standard deviations (SD) or median values. Categorical variables are presented as frequency counts with percentages. Categorical and continuous variables were compared between groups using the χ^2 test and Student's t-test respectively. Missing data were not replaced and were included in the denominator when calculating percentages.

All statistical analyses were performed using SAS software Version 9.4 (SAS Institute, Cary, United States).

2.4. Ethical considerations

The survey was conducted in accordance with relevant current French and international legislation and Good Epidemiological Practice guidelines. Since the patients' identity did not appear on the study questionnaires and patient management was not affected by participation in the study and all patient data were anonymised prior to entry into the study database, submission to an Institutional Review Board for ethical approval was not required. The physicians were required to give a letter of information to potentially eligible patients, who were given the opportunity to agree or refuse to participate in the survey. Refusal to participate had no impact on the patient's future care. The letter of information included a summary of the recommendations of the French Data Protection Authority (*Commission Nationale de l'Informatique et des Libertés*; CNIL) on the protection of personal data and the processing of the data from the survey.

3.1. Participating physicians

Of the 2564 neurologists invited to participate in the study, 192 agree to participate. For the 322 neurologists who replied to the invitation but declined to participate, the principal reasons for non-participation were that they did not see patients with MS (31.1%), lack of time (30.2%) and that they do not participate in studies (11.2%). One hundred and thirty-two participating centres were opened of whom 71 recruited at least one patient.

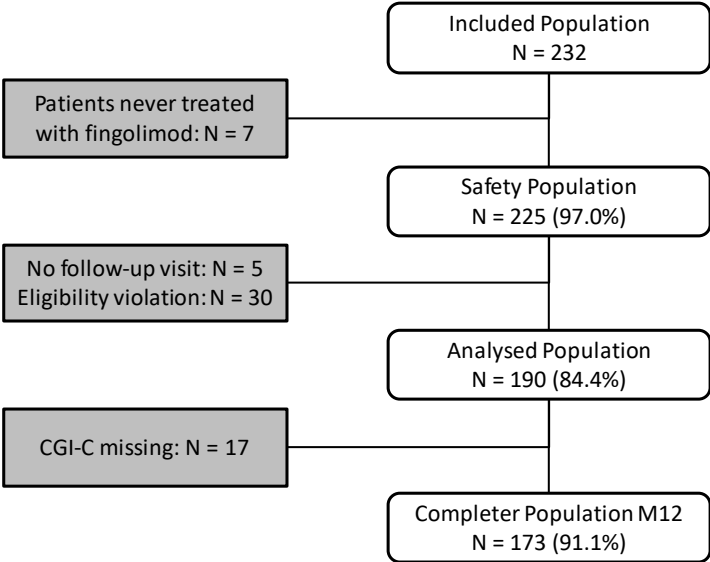
3.2. Patients

Participating neurologists included 232 patients (Included Population), of whom 201 (86.6%) attended visit M12 and thus completed the study. The Safety Population included 225 patients and the Analysis Population 190 patients. The distribution of patients across the different study populations is illustrated in Fig. 1. Seven of the enrolled patients were not prescribed fingolimod at the inclusion visit and are thus excluded from the Safety and Analysis Populations. A further 30 patients presented at least one violation of the eligibility criteria (certain patients presented more than one violation). These principally involved

receipt of more than one DMT for longer than six months before the switch to fingolimod (N = 18), a treatment duration for the previous DMT of <6 months (N = 12), switching to fingolimod >4 weeks prior to the inclusion visit (N = 8), a missing EDSS score at inclusion (N = 5) and no previous DMT treatment (N = 4).

Figure 1

Patient flow diagram.



Percentages are calculated with respect to the previous line of the flow chart. CGI-C: Clinical Global Impression – Change.

During the twelve-month follow-up period, thirty patients (13.7%) interrupted treatment with fingolimod. This was principally due to the occurrence of adverse events (nine patients), or to inadequate efficacy (ten patients). The mean duration of fingolimod treatment was 10.9 months (SD: 3.0; median: 11.8 months; range: 0.5 – 17.9).

The characteristics of the Analysis Population are presented in Table 1. The mean time since diagnosis was six years. The majority of patients (89.6%) presented clinical or radiological signs of disease activity in the previous twelve months in spite of their DMT therapy. The DMTs that were most frequently switched were β -interferons (42.6%), glatiramer acetate (16.8%), dimethylfumarate (16.8%) and teriflunomide (13.2%).

Table 1

Sociodemographic and clinical characteristics of the study population.

	Analysis Population [N = 190]
Age (mean \pm SD; years)	39.5 \pm 10.2

Gender (women, n,%)	142 (74.7%)
Time since diagnosis (mean \pm SD; years)	6.0 \pm 5.8
EDSS score at inclusion	
Not measured at inclusion visit	14 (7.4%)
Measured during an exacerbation	22/176 (12.5%)
Mean \pm SD	2.0 \pm 1.3
<3	130/176 (73.9%)
\geq 3	46/176 (26.1%)
Exacerbations in previous 12 months	
None	63 (33.2%)
One	90 (47.4%)
Two or more	37 (19.5%)
MRI in previous 12 months	177 (93.7%)
Disease activity visible	127/177 (71.8%)
Gd-enhancing T1 lesions only	11/127 (8.7%)
New T2 lesions only	50/127 (39.4%)
Both types of lesions	66/127 (52.0%)
Disease activity in previous 12 months ¹	
Both clinical and radiological activity	84 (44.4%)
Clinical activity only	42 (22.2%)
Radiological activity only	43 (22.8%)
Neither type of activity	20 (10.6%)
MRI data unavailable	1
Previous DMT \geq 6 months	
Interferon- β 1a <i>im</i>	48 (25.3%)
Interferon- β 1a <i>sc</i>	19 (10.0%)
Interferon- β 1b <i>sc</i>	14 (7.4%)
Glatiramer acetate	32 (16.8%)
Dimethylfumarate	32 (16.8%)
Teriflunomide	25 (13.2%)
Natalizumab	10 (5.3%)
Other	10 (5.3%)

¹Clinical activity was defined as at least one exacerbation in the previous 12 months. Radiological activity was defined as at least one Gd-enhancing T1 lesion or new T2 lesion in the previous 12 months.

DMT: disease modifying treatment; EDSS: Expanded Disability Status Scale; Gd: gadolinium; MRI: magnetic resonance imaging; SD: standard deviation.

3.3. Reasons for stopping previous treatment

The reasons given by the neurologist for switching treatment are presented in Table 2. Multiple reasons could be provided on the e-CRF and the response modalities were thus not mutually exclusive. The most frequent reason for switching observed in 84.7% of patients was clinical or radiological activity, or progression of clinical disability. Twenty patients had no clinical or radiological signs of disease activity in the year preceding inclusion. The second most frequent class of reasons, accounting for 30.5% of switches were related to the patients' preference, notably fatigue and a desire to change or lassitude with the previous treatment. Adverse events were cited for 18.4% of switches and the mode of administration for 12.1%.

Table 2

Reasons for switching treatment.

Reason for switching treatment	Analysis Population [N = 190]
Disease worsening	161 (84.7%)
New lesions (Gd-enhancing T1 or T2)	117 (61.6%)
New exacerbations	103 (54.2%)
Increase in EDSS score	31 (16.3%)
Persistent clinical symptoms	24 (12.6%)
Patient preference	58 (30.5%)
Patient complaint	48 (25.3%)
Fatigue	35 (18.5%)
Desire to change treatment	25 (13.2%)
Depression	8 (4.2%)
Cognitive problems	7 (3.7%)
Urinary problems	5 (2.6%)
Lassitude with taking treatment	18 (9.5%)
Reduction in activities of daily life	14 (7.4%)
Impact on lifestyle	5 (2.6%)
Adverse events	35 (18.4%)
Influenza-like symptom	19 (10.0%)
Injection-site reactions	13 (6.8%)

Gastrointestinal disorders	4 (2.1%)
Hot flushes	4 (2.1%)
Lymphopœnia / leucopœnia	3 (1.6%)
Lipodystrophy	1 (0.5%)
Alopecia	None
Treatment modality	23 (12.1%)
Route of administration	21 (11.1%)
Frequency of administration	10 (5.3%)
JC virus status	12 (6.3%)

Multiple reasons for switching were frequently given and no attempt was made to classify these as more or less important. This was most often the case when patient preferences were cited. For these 58 patients, disease worsening was also cited in 43 cases (74.1%) and adverse events in 19 cases (32.8%). On the other hand, for the 161 patients switching for disease worsening, multiple reasons were less frequently cited, with adverse events also being cited in 24 cases (14.9%), patient preferences being cited in 43 cases (26.7%).

3.4. Clinical evolution over the study period

During the follow-up period, 38 patients (20.0%) experienced at least one exacerbation, six patients experienced two relapses, four patients experienced three and two patients experienced four. The mean EDSS score did not change over the twelve-month study period (mean EDSS score at inclusion: 2.0 ± 1.3 versus 2.0 ± 1.5 at M12). For the 137 patients for whom the EDSS was evaluated at both inclusion and M12, the mean change in EDSS score was -0.1 ± 0.9 , the score was identical on both occasions for 68 patients (49.6%), whereas it had increased in 29 patients (21.2%) and decreased in 40 patients (29.2%). For the 173 patients who attended both the inclusion and the M12 visit, 99 patients underwent an MRI examination and ongoing disease activity was observed in 27 cases (three with Gd-enhancing T1 lesions only, fourteen with new T2 lesions only and ten with both types of lesion).

3.5. Clinical Global Impression - Change at M12

A completed CGI-C was available at M12 for 173 patients (91.1%). The modal response on the CGI-C was 'No change' (Response 4), accounting for 48.0% of patients overall (N = 83). Response 3 ('Minimally improved') accounted for 27.7% of patients and Response 5 ('Minimally Worse') for 11.6% of patients (Table 3). The other response modalities accounted for <10% of patients each. Overall, 67 patients (38.7%) were considered to be improved and 23 (13.3%) to have worsened.

No obvious differences were observed in CGI-C ratings as a function of the reason for switching (Fig. 2). Nonetheless, compared to the other two groups, when patient preferences entered into the decision, the proportion of patients who were considered minimally improved was somewhat higher (37.7% versus 27.6% and 25.8%) and the proportion considered unchanged was somewhat lower (41.5% versus 49.7% and 51.6%).

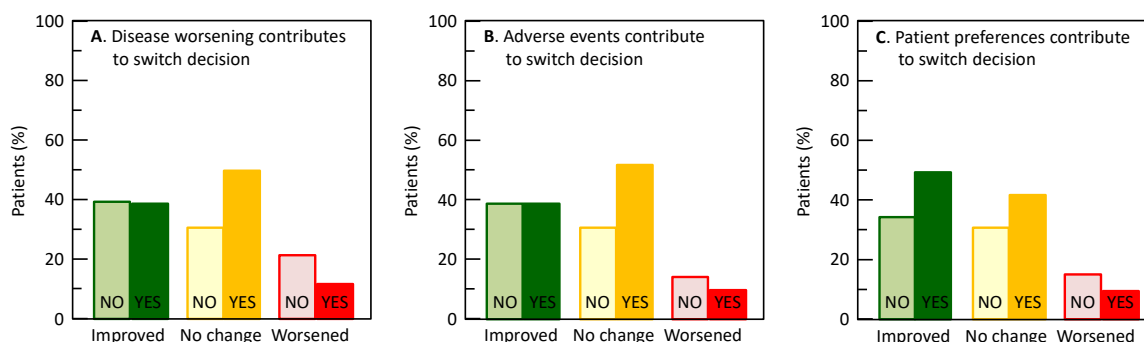
Table 3

CGI-C and PGI-C ratings at 12 months, overall and by reason for switch

	CGI-C (N = 190)				PGI-C (N = 190)
	Missing data				
	17				56
	Disease worsening	Adverse events	Patient preferences	All completer population	All completer population
	(N = 145)	(N = 31)	(N = 53)	(N = 173)	(N = 134)
1. Very much improved	2 (1.4%)	0 (0.0%)	1 (1.9%)	2 (1.2%)	7 (5.2%)
2. Much improved	14 (9.7%)	4 (12.9%)	5 (9.4%)	17 (9.8%)	31 (23.1%)
3. Minimally improved	40 (27.6%)	8 (25.8%)	20 (37.7%)	48 (27.7%)	37 (27.6%)
4. No change	72 (49.7%)	16 (51.6%)	22 (41.5%)	83 (48.0%)	41 (30.6%)
5. Minimally worse	15 (10.3%)	3 (9.7%)	5 (9.4%)	20 (11.6%)	16 (11.9%)
6. Much worse	2 (1.4%)	0 (0.0%)	0 (0.0%)	3 (1.7%)	2 (1.5%)
7. Very much worse	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Figure 2

Clinical Global Impression – Change at 12 months.



3.6. Patient Global Impression - Change at M12

The PGI-C was completed at M12 and returned by 145 patients (83.8% of the Completer Population). As with the CGI-C, 'No change' was the most frequent response modality (Table 4). However, more patients rated themselves improved on the PGI-C than were rated as improved by the physician. For the 132 patients (69.5%) for whom both the CGI-C and the PGI-C were available at M12, ratings were compared between the two measures, grouped into three categories (improved, no change and worsened). For the majority of these patients (N = 91; 62.8%), the two ratings were identical. However, of the 64 patients rated as 'no change' by the physicians on the CGI-C, 21 (32.8%) rated themselves as 'improved' and 10 (15.6%) as 'worsened'. The overall level of agreement was moderate ($\kappa = 0.48$ [95% CI: 0.35 – 0.60]).

Table 4

Correlation between ratings on the CGI-C and PGI-C at M12.

	PGI-C at M12			
CGI-C at M12	Improvement	No change	Worsening	TOTAL
Improvement	51	7	0	58
No change	21	33	10	64
Worsening	2	1	7	10
TOTAL	74	41	17	132

Data are presented for the 132 patients for whom both questionnaires were available.

3.7. ACCEPT[®] questionnaire

The mean dimension scores on the ACCEPT[®] scale at the inclusion visit, reflecting acceptability of the previous DMT ranged from 36.7 for the effectiveness dimension to 72.2 for medication inconvenience (Table 5). The mean general acceptability score was 42.7 [95%CI: 34.5 – 50.9]. At the M12 visit, mean dimension scores had risen for all dimensions with the exception of long-term treatment and numerous medications; they now ranged from 63.4 for effectiveness to 96.8 for medication inconvenience. The mean general acceptability score at M12 was 64.6 [95%CI: 57.6 – 71.6].

Table 5ACCEPT[®] questionnaire scores.

Dimension	Inclusion visit	Visit M12
<i>Missing data</i>	<i>N = 65</i>	<i>N = 87</i>
Medication inconvenience	72.2 [65.0 – 79.4]	96.8 [95.1 – 98.6]
Long-term treatment	63.5 [57.8 – 69.2]	67.6 [64.8 – 70.4]
Regime Constraints	68.6 [61.9 – 75.3]	85.5 [81.7 – 89.3]
Numerous medications*	2.7 [2.55 – 2.85]	2.8 [2.7 – 2.9]
Side-effects	67.7 [60.5 – 74.9]	85.4 [81.4 – 89.4]
Effectiveness	36.7 [28.0 – 45.4]	63.4 [55.8 – 71.0]
General	42.7 [34.5 – 50.9]	64.6 [57.6 – 71.6]

*This single-item dimension is scored on a scale of 0 – 3, rather than 0 – 100 for the remaining dimensions.

3.8. Safety

During the 12-month follow-up period, 238 adverse events were reported for 130 patients in the Safety Population (57.8%). The most frequently-reported adverse events were lymphopenia (75 events in 66 patients; 29.3%), increased γ -glutamyl-transferase (8 events in 8 patients; 3.6%), hepatocellular injury (8 events in 8 patients; 3.6%) and headaches (7 events in 7 patients; 3.1%). No other individual adverse event was reported in >3% of patients. Twenty patients (8.9%) presented a total of 32 serious adverse events, of which 23 events in fourteen patients were considered treatment-related. These are listed in Table 6. The most frequent of these treatment-related serious adverse events were lymphopenia, bradycardia and hepatocellular injury (three patients each) and increased γ -glutamyl-transferase (2 patients).

Table 6

Adverse events

System-organ class and Preferred Term	Number of events	Number of patients (%)
Any adverse event	238	130 (57.8%)
Any serious adverse even	32	20 (8.9%)
Any adverse event leading to treatment discontinuation	41	34 (15.1%)

Any treatment-related adverse event	146	97 (43.1%)
Any treatment-related serious adverse event	23	14 (6.2%)
Lymphopenia	7	3 (1.3%)
Bradycardia	3	3 (1.3%)
Hepatocellular injury	3	3 (1.3%)
γ-Glutamyl transferase increased	2	2 (0.9%)
Atrioventricular block	1	1 (0.4%)
Blood alkaline phosphatase increased	1	1 (0.4%)
Liver function test increased	1	1 (0.4%)
Cerebrovascular accident	1	1 (0.4%)
Reversible cerebral vasoconstriction syndrome	1	1 (0.4%)
Macular oedema	1	1 (0.4%)
Groin abscess	1	1 (0.4%)
Drug ineffective	1	1 (0.4%)

4. Discussion

The goal of this study was to document patient outcome following switching from a first DMT to fingolimod according to the reason for switching. Although multiple reasons were given for switching, lack of efficacy of the first-line treatment contributed to the decision in 85% of cases. This is not particularly surprising since it corresponds to the specific approved indication for fingolimod, and is a treatment strategy for which there is strong evidence for benefit (Hansen et al., 2015; Lebrun-Frenay et al., 2019; Miller, 2016). At inclusion, 72% of patients evaluated on MRI had visible disease activity and 67% had experienced at least one exacerbation in the previous year, in spite of taking a first-line DMT. The data suggest that around twenty percent of patients are being switched treatment on the basis of radiological evidence for disease activity only, in keeping with a treatment goal of 'no evidence for disease activity' (NEDA) (Havrdova et al., 2010). Only twenty patients with NEDA at inclusion were switched to fingolimod, which indicates that fingolimod is not being widely prescribed outside of its approved indication of '*patients with highly active RRMS despite a full and adequate course of at least one DMT*'. Since this study only included patients who were switched to fingolimod, it is not possible to know the proportion of patients who had evidence for disease activity that were not switched.

Only a minority of patients were switched due to the occurrence of adverse events, and this was rarely the only reason for the switch. This may reflect the tendency of neurologists to switch a patient whose first-line treatment is poorly tolerated to an alternative first-line DMT, as has been described in the Italian cohort of Saccà *et al.* (Saccà et al., 2019). Another recent Italian cohort of patients who switched between DMTs (Patti et al., 2020) reported that the principal reason for switching was inadequate efficacy and that less than ten percent of patients were switched principally due to the preference of the patient. The reasons for switching identified in the present study are consistent with this hierarchy.

In thirty percent of cases, patient preferences contributed to the decision to switch, although this was not the only reason for most of these. Lassitude with taking the current DMT and a desire to change treatment were frequently cited, together with symptoms of MS such as fatigue. On the other hand, the mode of administration (route or frequency) contributed to the decision to switch in only 12% of cases. This may indicate that neurologists and patients are prepared to continue with injectable therapy as long as disease activity is under control.

Twelve months after the switch to fingolimod, 39% of patients were considered by the physician to be improved and 48% were considered unchanged. It should be noted that the CGI was originally developed for use in psychiatric disorders which present with episodic fluctuating symptoms where the treatment goal is symptom resolution, and not for

neurodegenerative diseases such as multiple sclerosis, where the goal is to minimise disease activity and to prevent worsening of the clinical state. This may explain the high proportion of patients rated as unchanged, whereas, objectively, control of disease activity in these highly active patients was improved following the switch, with 80% of patents being exacerbation-free at M12, and 73% of patients who underwent a post-switch MRI having no signs of new disease activity. It is also possible, at least in patients switched for disease worsening, that ‘regression to the mean’ of disease activity following an active phase at the time of the switch may account for some of the improvement observed. Without complete information of patient history, the extent of such regression to the mean cannot be determined.

There were no major differences in the CGI-C ratings according to the reason of the switch, with the exception of a somewhat higher proportion of patients who improved in the group of patients in whom patient preferences contributed to the reasons for switch. It may be hypothesised that these patients, who were dissatisfied with their previous treatment, may be more adherent to fingolimod than to their first-line DMT, and therefore benefit more from it.

Patients were also asked to rate their impression of change following switch with the PGI-C. Although the overall correlation between physician and patient ratings was respectable, patients less frequently rated themselves as unchanged than did their physicians, with around half of patients considering themselves improved.

The study provided an opportunity to evaluate treatment acceptability using the ACCEPT[®] questionnaire. Although patients with MS were evaluated during the validation of this questionnaire (Lambert et al., 2018), the ACCEPT[®] has not yet been used in a dedicated study in MS, nor to evaluate changes in treatment acceptability following treatment switches. An increase in around twenty points in acceptability scores was observed following switch for all dimensions with the exception of the ‘long-term treatment’ and ‘numerous medications’ items. Low scores prior to the switch are to be anticipated, since the previous treatment was considered for whatever reason inadequate. The creators of the ACCEPT[®] questionnaire did not provide any guidance on how the scores should be interpreted, nor on what would constitute a clinically-significant change. In their description of the questionnaire, mean general scores in different chronic diseases ranged from 33.7 for fibromyalgia to 61.2 for type 1 diabetes, with a mean score for MS, in an unselected population, of 48.6. In the present study, the mean general score at inclusion was 42.7, somewhat lower than the value observed in the validation study, but increased to 64.6 twelve months after switching to fingolimod, which is higher than the mean scores for all the diseases evaluated in the validation study. This value is close to the highest mean value reported in the validation study. This difference between scores at inclusion and twelve

months was of similar magnitude as the difference in treatment acceptability observed in the validation study between, for example, treatments for breast cancer (mean score ~38) and those for hypertension (mean score ~55). Moreover, the mean medication inconvenience score in our patients, most of whom switched from an injectable to an oral treatment, rose to 96.8, which is close to the maximum possible score and to the score in the highest rated disease (hypertension; mean score: 96.3) in the validation study. The increase in medication inconvenience score was around 25 points, which is a larger difference than the difference in mean scores between sixteen of the nineteen diseases evaluated in the validation study. These indirect comparisons would suggest that the changes in ACCEPT scores observed following a switch to fingolimod are clinically relevant.

With respect to safety, the adverse event profile was similar to that described in the Phase III randomised clinical trials (Cohen et al., 2010; Kappos et al., 2010). No unanticipated safety issue or new signal of potential risk was identified.

The study has several limitations, which are principally related to the observational nature of the study. Firstly, inclusion bias cannot be excluded. Neurologists were expected to include consecutively the first four patients fulfilling the eligibility criteria, but there was no requirement to complete a patient registry of all consulting patients, so there is no way of ensuring that this happened nor whether patients who were included were representative of all eligible patients. However, the demographic and clinical features of the included patients are similar to those of a large registry of patients treated with fingolimod in France enrolled over a similar period (Castelnovo et al., 2019). Likewise, it is not possible to be sure that the decision to switch patients to fingolimod was made independently of study participation. The second limitation is the relatively large amount of missing data, particularly for the questionnaire. At the twelve-month visit, the CGI-C was not completed for 9% of patients, the PGI-C for 27% and the ACCEPT[®] for 46%.

In conclusion, most patients who switch from a first DMT to fingolimod do so for reasons of persistent disease activity during the initial treatment, although patient preferences enter into the decision in around one third of cases. The switch to fingolimod is followed by a reduction in disease activity, perceived improvement in the clinical state of the patient and improved acceptability of treatment.

Data availability

Anonymised data will be made available to qualified external researchers, with requests reviewed and approved by an independent review panel on the basis of scientific merit.

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Competing interests

AT has received consultancy or speaker's fees from Medday Pharmaceuticals, Biogen, Novartis, Hikma and Roche.

CP has received compensation as a consultant, advisory board member, or speaker, for Roche, Novartis, Biogen, Teva, Sanofi Aventis, Genzyme

PT has received consulting and lecturing fees and travel grants from Biogen, Genzyme, Novartis, Merck Serono, Teva Pharma, Sanofi Aventis, and Roche.

CM has participated in scientific advisory boards for Novartis, Teva, Biogen, Sanofi, Genzyme, Bayer, Merck, Eisai, and Lilly, and spoken at or chaired scientific meetings for Novartis, Teva, Biogen, Merck, Genzyme, Bayer, BMS, Pfizer and GSK.

IC, BD, FL, MM and KR are employee of Novartis, a pharmaceutical company that developed and markets fingolimod.

Author's contributions

AT: Conceptualisation, methodology, investigation, validation, writing - review & editing.

CP: Conceptualisation, methodology, investigation, validation, writing - review & editing.

PT: Conceptualisation, methodology, validation, investigation, writing - review & editing.

KR: Conceptualisation, writing - review & editing.

MM: Conceptualisation, funding acquisition, project administration.

BD: Project administration, supervision, validation, writing - review & editing.

FL: Project administration, validation, writing - review & editing.

IC: Conceptualisation, funding acquisition, writing - review & editing.

CM: Conceptualisation, methodology, investigation, validation, writing - review & editing.

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