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Baseline characteristics associated with NEDA-3 status in fingolimod-treated patients with relapsing-remitting multiple sclerosis

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Abstract

Background: Fingolimod is an efficacious treatment for relapsing-remitting multiple sclerosis (RRMS) and there is class I evidence that it is superior to standard care in reducing relapse rate. However, real-world data investigating its effectiveness and potential predictors of response are still scarce.

Objective: To estimate (i) the proportion of fingolimod-treated patients who achieved the no evidence of disease activity (NEDA-3) status; and (ii) to determine which baseline (i.e. at treatment start) clinical and magnetic resonance imaging (MRI) variables were associated with better outcomes.

Methods: We collected clinical and MRI data of RRMS patients treated with fingolimod and followed-up for 24 months. The proportion of patients who had NEDA-3 - i.e. absence of relapses, sustained Expanded Disability Status Scale (EDSS) worsening and radiological activity on MRI - was estimated. A Cox proportional hazard model was carried out to investigate which baseline characteristics were associated with the NEDA status at follow-up.

Results: We collected data of 201 patients who started fingolimod. Of them, 24 (12%) were treatment-naïve, 115 (58%) were switched after failing a self-injectable drug, and 60 (30%) switching from natalizumab. Five patients who discontinued fingolimod early (within 3 months) (bradycardia, $n = 2$; leukopaenia, $n = 2$; macular oedema, $n = 1$) were removed from the analysis. At follow-up, 118 (60%) patients achieved the NEDA-3 status, while 78 experienced clinical and/or MRI activity. The risk of not achieving the NEDA-3 status was associated with higher baseline EDSS score (hazard ratio [HR] = 1.18, $p = 0.024$) and more relapses in the 12 months prior to fingolimod start (HR = 1.61, $p = 0.014$).

Conclusion: Our findings suggest that fingolimod may lead to a better control of the disease if started in patients with a less aggressive disease (i.e. fewer pre-treatment relapses and milder disability level), thus supporting its possible role as an early treatment for MS.

Keywords: Multiple sclerosis [190], Clinical outcome measures [40], Therapeutics [360], Fingolimod

Background

Multiple Sclerosis (MS) is a chronic, inflammatory, demyelinating, immune mediate disease of the central nervous system (CNS) that affects almost 2.1 million people worldwide. At least 70–75% of these patients are suffering from the relapsing-remitting type of MS (RRMS) that is characterized by acute inflammatory episodes of CNS demyelination [1]. Relapses may be also associated with disability worsening [2], therefore the main therapeutic aim in RRMS is to control disease activity by reducing the number of relapses and preventing disability progression [3]. Relapses and disability worsening assessed by the Expanded Disability Status Scale (EDSS) [4] are indeed currently accepted as main endpoints in large, phase III, randomized clinical trials [5]. More recently, the No Evidence of Disease Activity (NEDA-3) has been proposed as a new outcome measure for RRMS based on (i) absence of relapses; (ii) absence of sustained disability worsening, defined as ≥1-point

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increase in EDSS score confirmed 3-6 months apart; (iii) absence of radiological activity, seen on magnetic resonance imaging (MRI) as gadolinium-enhancing lesions or new/enlarged T2-hyperintense lesions [6].

Fingolimod 0.5 mg (Gilenya®, FTY720, Novartis Pharma AG, Basel Switzerland) is a sphingosine-1-phosphate receptor modulator which has been approved as once daily orally administered therapy for RRMS [7]. As evidenced by the phase III trials FREEDOMS, FREEDOMS II and TRANSFORMS, fingolimod significantly reduces relapses rate compared with both placebo and intramuscular Interferon beta (IFNB)-1a [8–10]. Moreover, fingolimod is superior to both placebo and IFNB-1a with regard to MRI-related measures, namely the number of new or enlarged lesions on T2-weighted images, gadolinium-enhancing lesions, and brain-volume loss [7–9]. A post-hoc analysis of the FREEDOMS trial also demonstrated a higher proportion of patients treated with fingolimod achieving the NEDA-3 status than those treated with placebo (33 vs. 13%) [11].

However, real world data on the effectiveness of fingolimod are still scarce and post-marketing studies were mainly designed to either compare fingolimod with other DMTs (self-injectable drugs, natalizumab, dimethyl fumarate) [12–20] or investigate the role of fingolimod as an exit strategy after natalizumab discontinuation [21–27]. Therefore, here we aimed at estimating the proportion of patients achieving the NEDA-3 status in a real-world population. Baseline characteristics associated with a better chance to achieve the NEDA-3 status were also investigated.

Methods

Study design and participants

This was a 24-month, retrospective, independent, single-centre, post-marketing, study. Given its retrospective design, this study in no way interfered in the care received by patients. The present study was conducted in accordance with specific national laws, the International Conference on Harmonization Guidelines of Good Clinical Practice and the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

We collected clinical and MRI data of patients with RRMS according to revised McDonald criteria [28] and starting treatment with fingolimod at the MS Centre of S. Andrea Hospital in Rome according to the Italian regulatory criteria. Only patients having a regular follow-up for at least 24 months from fingolimod start were included in the present study.

Demographic and clinical information were collected at baseline visit (i.e. at fingolimod start) and included sex, time since first symptom, number of exacerbations in the previous year, EDSS score, treatment history, presence of contrast-enhancing lesions at MRI scan of brain and spinal cord.

Ethical standard

This study was conducted in accordance with the International Conference on Harmonization Guidelines of Good Clinical Practice and the Declaration of Helsinki. In no way did this study interfere in the Care received by patients. The Ethical Committee of Sapienza University provided exemption of approval for post-authorisation observational studies. Each patient involved in this study signed an informed consent before collecting, storing and analysing individual data.

Follow-up assessments

Clinical relapses and changes in EDSS score during treatment, as well as any other medical event occurred as a result of fingolimod treatment, were recorded.

We collected also MRI data after approximately 6, 12, and 24 months of fingolimod treatment, focusing on the presence of gadolinium-enhancing lesions on post-contrast T1-weighted scans and the appearance of new hyperintense lesions on T2-weighted sequences (when compared to the previous scan). Unscheduled MRI scans were also performed, if necessary, to confirm suspect relapses.

To ensure a more reliable comparison between each scan, images were acquired in the same outpatient centre using a superconducting 1.5 T magnet (GE Excite), according to published guidelines [29]. Reproducible slice positioning was maintained throughout the follow-up using the same anatomical landmarks for each patient. All MRI scans were interpreted by experienced radiologists unaware of clinical data.

Outcome measures

As primary outcome, we estimated the proportions of patients who achieved the NEDA-3 status at the end of the 24-month follow-up. As mentioned, NEDA-3 is a combined measure defined as absence of either a clinical relapse, or disability worsening, or radiological activity [6]. The NEDA-3 has been recently proposed as a principal aim in management of relapsing MS because it leads to better long-term outcomes [6–30].

We also analyzed individually the subcomponents of disease activity as secondary outcomes (time to relapse, disability worsening, radiological activity).

A relapse was defined as the appearance or reappearance of one or more symptoms attributable to MS, accompanied by objective deterioration on neurological examination lasting at least 24 h, in the absence of fever and preceded by neurological stability for at least 30 days [28].

Disability worsening was defined as ≥1.5-point increase (if baseline EDSS score was 0), ≥1.0-point

increase (if baseline EDSS score was <5.5), or ≥0.5-point increase (if baseline EDSS score was ≥5.5) confirmed 6 months apart [31].

Radiological activity was defined as the occurrence of ≥1 GD-enhancing lesion or ≥1 new T2-hyperintense lesion. We decided to not consider enlarged T2-hyperintense lesions since a previous study demonstrated a poor between-rater agreement for this metric under routine clinical setting [32].

Statistical Analyses

All values are expressed as mean (standard deviation, SD), median (range), or proportion, as appropriate.

We considered the following baseline (i.e. at fingolimod start) characteristics: sex, age, time since first symptom, EDSS score, number of relapses in the previous 12 months, presence of gadolinium-enhancing lesions at brain MRI scan. The multiple sclerosis severity score (MSSS) was also estimated for each participant to obtain a variable accounting for the disease severity [33].

Patients were also divided according to their treatment history as 'treatment-naïve', 'switchers for failure', i.e. switching from self-injectable DMTs, 'switchers for safety', i.e. switching from natalizumab. Between-subgroup differences were tested using the Kruskall-Wallis test and the Chi-squared test for continuous and dichotomous variables, respectively.

A time-to-event multivariable model was performed to investigate which baseline characteristics were associated with NEDA-3 status and its subcomponents at the end of the 24-month follow-up. Specifically, we inserted the counterpart of NEDA-3 (i.e. the occurrence of any evidence of disease activity, such as relapses, disability worsening and/or radiological activity) as dependent variable in a Cox proportional hazards regressions. The aforementioned baseline patients' characteristics and interaction terms were added in the model as independent variables in a stepwise fashion (for predictor inclusion: $F \geq 1$ and $p \leq 0.05$; for exclusion: $F < 1$ and $p > 0.10$). As main time variable we used the length of the observation (in months), between the baseline and the last visit over the 24-months period, or outcome reach, whichever came first.

Patients lost to follow-up and those who discontinued fingolimod within the first three months of treatment were excluded from the main analysis. A post-estimation sensitivity analysis was also done by applying the best-case scenario (i.e. the NEDA-3 status) and worst-case scenario (i.e. any evidence of disease activity due to relapses, and disability worsening and/or radiological activity) to patients who were excluded from the case-base analysis.

All p-values less than 0.05 in either directions were considered as significant. Analyses were carried out using a PC version of Statistical Package for Social Sciences 16.0 (IBM SPSS, Chicago, IL, USA).

Results

Participants

The Table 1 shows the baseline characteristics of patients. We analysed data of 201 patients (141 females, 60 males) with mean (SD) age of 37.9 (9.4), mean time since first symptom of 8.8 (5.9) years, and median EDSS score of 2.0 (range 0–6.5). Twenty-four (12%) patients were treatment-naïve, 117 (58%) were switched after failing a first-line DMT, and 60 (30%) were switched from natalizumab treatment due to safety reasons (i.e. they were tested positive for the John Cunningham virus and then were considered at high risk for developing Progressive Multifocal Leukoencephalopathy). There were significant between-subgroup differences across patients with different treatment history. The time since first symptom was shorter in treatment-naïve patients than in both switchers for failure ($p < 0.05$) and switchers for safety ($p < 0.001$).

The disability level, assessed by EDSS score, was higher in switchers for safety than in both switchers for failure ($p < 0.001$) and treatment-naïve ($p < 0.05$). The number of relapses in previous year was lower in switchers for safety than in both switchers for failure ($p < 0.05$) and treatment-naïve ($p < 0.05$). Sex, age, presence of gadolinium-enhancement at baseline MRI scan did not differ between subgroups defined by treatment history.

Five (2.5%) patients who discontinued fingolimod within 3 months from treatment start were removed from subsequent analyses. They were discontinued early for the following reasons: bradycardia, $n = 2$; leukopaenia, $n = 2$; macular oedema, $n = 1$. There was no patient lost to follow-up.

Study outcomes

The Fig. 1 shows the proportion of patients who achieved the NEDA-3 status at the end of the 24-month follow-up. At follow-up, 118 (60%) patients achieved the NEDA-3 status; 149 (76%) were free from relapses; 168 (86%) were free from disability worsening; 135 (69%) were free from radiological activity.

Among the 78 patients who had any evidence of disease activity, 15 experienced relapses, disability worsening and radiological activity; 23 relapsed with concomitant radiological activity, but without disability worsening; three relapsed with subsequent disability worsening, but without evidence of radiological activity; 1 had MRI activity and subsequent disability worsening, but without any evident clinical exacerbation; the remaining 36 patients had only either relapses ($n = 8$), disability worsening ($n = 8$), or radiological activity ($n = 20$).

Table 1 Baseline characteristics of patients ($n = 201$)

	Whole sample	Tretament-naive	Switchers for failure	Switchers for safety	
N	201	24	117	60	
Gender, *n* (%)					
Female	141 (70)	17 (71)	88 (75)	36 (60)	
Male	60 (30)	7 (29)	29 (25)	24 (40)	
Age, years					
mean (SD)	37.9 (9.3)	37.2 (8.0)	37.5 (9.9)	39.0 (8.5)	
median [range]	38 [18–60]	37 [20–53]	38 [18–60]	39 [18–60]	
Time since first symptom, years					*
mean (SD)	8.8 (6.0)	5.1 (5.8)	8.2 (5.8)	11.3 (5.6)	
median [range]	8 [<1–23]	2 [<1–18]	7 [1–21]	11 [2–23]	
EDSS score					*
mean (SD)	2.7 (1.4)	2.5 (1.0)	2.4 (1.3)	3.4 (1.5)	
median [range]	2.0 [0–6.5]	2.0 [0–5.0]	2.0 [1.0–5.5]	3.5 [1.0–6.5]	
No. of relapses in previous year					*
mean (SD)	1.1 (0.6)	1.3 (0.5)	1.2 (0.4)	0.9 (0.8)	
median [range]	1 [0–3]	1 [1, 2]	1 [1–3]	1 [0-3]	
Presence of gadolinium-enhancing lesions, *n* (%)	125 (62)	17 (71)	78 (67)	30 (50)	

*$p < 0.01$ by the Kruskal-Wallis test

Baseline variables associated with NEDA-3 status

Previous treatment history affected the chance of NEDA-3 at follow-up. We found indeed that the proportions of patients reaching the NEDA-3 status were 81% (17/21), 61% (70/115) and 52% (29/60) in treatment-naïves, switchers for failure and switchers for safety, respectively (see Fig. 2). However, only the comparison between treatment-naïve and switchers for safety reached the statistical significance ($p = 0.02$ by the Chi-squared test), while there was a trend towards statistical significance by comparing treatment-naives and switchers for failure ($p = 0.08$). There was no difference between switchers for failure and switchers for safety ($p = 0.24$).

The Table 2 shows the findings of the Cox proportional hazard model for the NEDA-3 status in the case-

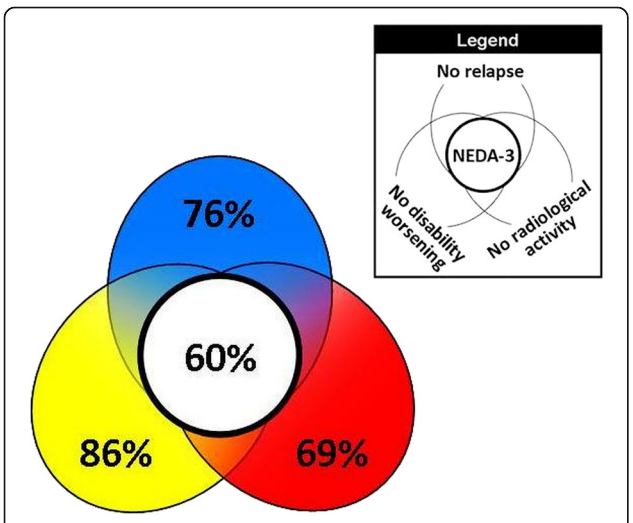

Fig. 1 Description of different components of no evidence of disease activity (NEDA-3) at the end of the 24-month follow-up in 196 patients with relapsing-remitting multiple sclerosis treated with fingolimod

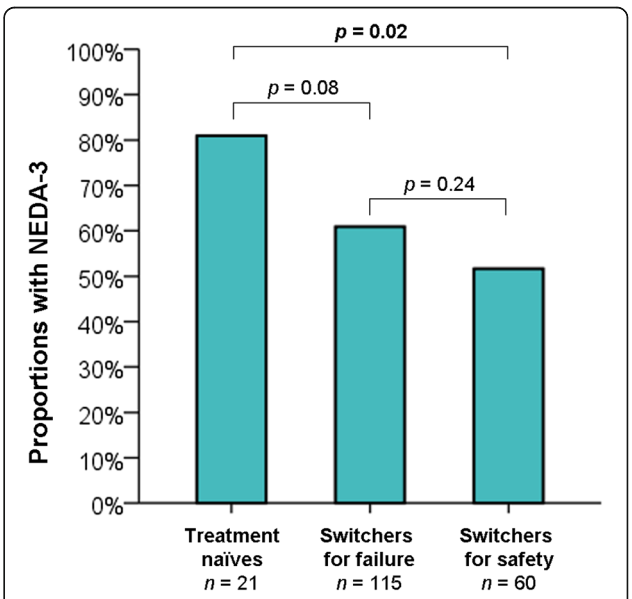

Fig. 2 Proportions of patients achieving the no evidence of disease activity (NEDA-3) at the end of the 24-month follow-up according to previous treatment history ($n = 196$); statistical comparisons were done by the Chi-squared test

Table 2 Stepwise Cox proportional hazard regression model showing baseline variables associated with evidence of disease activity (NEDA-3) at 24 months after fingolimod start ($n = 196$)

Independent variables	Hazard Ratio	95% confidence intervals	*P*-value
Expanded Disability Status Scale (EDSS) score (each step)	1.18	1.02–1.37	0.024
Relapses (each unit)	1.61	1.10–2.35	0.014

Inserted variables that did not contribute to fit the model were as follows: sex, age, time since first symptom, multiple sclerosis severity score (MSSS), presence of gadolinium–enhancing lesions at brain MRI scan.

Hazard ratios >1.0 indicates an increased risk of occurrence of any evidence of disease activity, i.e. relapses, disability worsening and/or radiological activity

base scenario ($n = 196$). We found an increased risk of not achieving the NEDA-3 status in patients who were more disabled (HR = 1.18, $p = 0.024$) and in those who experienced more relapses in the 12 months prior to fingolimod start (HR = 1.61, $p = 0.014$). Previous treatment history did not contribute to fit the model.

The post-estimation sensitivity analysis showed that all these estimates were not altered in the best-case and worst-case scenarios (data not shown).

Discussion

The aim of the present study was two-fold: estimating the proportion of patients achieving the NEDA status in a real-world population taking fingolimod and identifying baseline characteristics associated with a better outcome after 24 months of follow-up.

We found 60% of patients achieving the NEDA-3 status, an almost double proportion with respect to post-hoc analysis (33%) from the FREEDOMS trial [11]. This confirms data from other post-marketing studies showing that the effectiveness of DMTs for MS is often better than their efficacy [34]. A very similar proportion (60%) of patients achieving NEDA-3 was instead reported in a 4.5-year extension phase of TRANSFORMS trial after switching from IFNB-1a to fingolimod [35].

The discrepancy in proportions with NEDA-3 between experimental and real world setting might be explained by the different way to assess relapses, change in disability and radiological activity [5]. Most relapses were assessed retrospectively in our study, while new symptoms must have been coupled with an increase in EDSS score or functional systems to be defined as a qualified relapses in FREDOMS and TRANSFORMS trials [8, 9]. The time required to confirm disability worsening was 6 months in our study versus 3 months in RCTs. Another difference is that we did not consider enlarged T2 lesions in the assessment of MRI activity, since a previous study demonstrated a poor between-rater agreement for this metric under routine clinical setting [32].

As expected, patients switching from natalizumab (switchers for safety) were at higher risk of not achieving the NEDA-3 status [23]. We also found a trend ($p = 0.08$) towards a worse outcome in patients who switched from self-injectable DMTs (switchers for failure) with respect to treatment-naïve patients, supporting previous suggestions about the role of fingolimod as first treatment option [11, 20].

However, there were relevant baseline differences across subgroups of patients defined by previous treatment history that are known to act as treatment effect modifiers [36]. We found indeed that fingolimod may lead to a better control of the disease if started in patients with a less aggressive disease, i.e. fewer pre-treatment relapses and milder disability level, regardless of previous treatment history.

Our findings are partially in contrast with the subgroup analyses of the FREEDOMS and TRANSFORMS trials, where the pre-treatment number of relapses did not affect the on-treatment annualised relapse rate [37, 38] and patients with EDSS score ≤3.5 did not have a significant reduction in risk of disability progression compared to placebo [37]. Moreover, subgroup analysis of pivotal trials did not reveal any clear advantage for treatment-naïves with respect to previously treated patients, except for a higher relative reduction in relapse rate for treatment-naive rapidly evolving severe RRMS patients (i.e. patients who had ≥2 relapses within the year before baseline and ≥1 gadolinium-enhancing lesion at baseline) [37].

However, these contradictions are attributable to the intrinsic differences between the NEDA-3 status, based on the absolute absence of clinical and radiological activity, and outcomes considered in RCTs, based on quantitative differences in outcomes with respect to placebo or an active comparator [5, 6, 34]. Lastly, we have also to bear in mind that the potential predictors of response to therapy are indeed strictly dependent on the outcome measure considered as criterion of response [39].

Our study suffers from some limitations, mainly due its retrospective design and lack of control group. Despite the adoption of a very stringent outcome such as NEDA-3, we were not able to estimate brain volume loss, thus missing the chance to obtain data on NEDA-4; therefore our data are mainly weighted towards focal inflammatory activity rather than neurodegeneration processes [40]. Another drawback of our study is the short follow-up (24 months); in this regard, further effort is required to determine whether the NEDA-3 status achieved after 24 months of fingolimod may be sustained even in a longer-term follow-up. Long-term data

suggest indeed that the NEDA-3 status is difficult to maintain after 7–10 years from starting self-injectable DMTs, while a longer-term disease remission has been described with natalizumab, but with a greater burden in terms of health cost, surveillance, and averse events [30, 41, 42].

Conclusions

Our study suggests that patients with fewer pre-therapy relapses and milder disability level are the best candidates for a more effective treatment with fingolimod. We hope that these findings might contribute to a more accurate identification of patients likely to have the maximum benefit from the fingolimod treatment in real world practice, despite several biases due to the retrospective study design.

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Availability of data and materials
The dataset supporting the conclusions of this article is available upon reasonable request from the corresponding author.

Authors' contributions
MG: acquisition of the data, analysis and interpretation of the clinical data; AL: acquisition of the data, analysis and interpretation of the clinical data; LP: conception and design of the study, analysis and interpretation of the data; drafting a significant portion of the manuscript/figures; MNH: analysis and interpretation of the MRI data; CP: conception and design of the study, drafting a significant portion of the manuscript/figures. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
not applicable.

Ethics approval and consent to participate
The Ethical Committee of Sapienza University provided exemption of approval for post-authorisation observational studies. Each patient involved in this study signed an informed consent before collecting, storing and analysing individual data.

Disclosures
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