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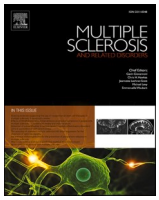

NEDA-3 achievement in early highly active relapsing remitting multiple sclerosis patients treated with Ocrelizumab or Natalizumab

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ABSTRACT

Background: in the early stages of Multiple Sclerosis (MS), initiating high-efficacy disease-modifying therapy (HE DMTs) may represent an optimal strategy for delaying neurological damage and long-term disease progression, especially in highly active MS patients (HAMS). Natalizumab (NAT) and Ocrelizumab (OCR) are recognized as HE DMTs with significant anti-inflammatory effects. This study investigates NEDA-3 achievement in treatment-naïve HAMS patients receiving NAT or OCR over three years.

Methods: we retrospectively enrolled treatment-naïve HAMS patients undergoing NAT or OCR, collecting demographic, clinical, and instrumental data before and after treatment initiation to compare with propensity score analysis disease activity, time to disability worsening, and NEDA-3 achievement.

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Results: we recruited 281 HAMS patients with a mean age of 32.7 years (SD 10.33), treated with NAT (157) or OCR (124). After three years, the Kaplan-Meier probability of achieving NEDA-3 was 66.0 % (95 % CI: 57.3 % - 76.0 %) with OCR and 68.2 % (95 % CI: 59.9 % - 77.7 %) with NAT without significant differences between the two groups ($p = 0.27$)
Discussion and conclusion: starting HE DMT with monoclonal antibodies for HAMS could achieve NEDA-3 in a high percentage of patients without differences between NAT or OCR.

1. Introduction

Multiple sclerosis (MS) is the most prevalent chronic inflammatory disease of the central nervous system (CNS) involving the brain and spinal cord. MS presents in two clinical forms: relapsing multiple sclerosis, manifesting with inflammatory attacks, and progressive MS, defined as the constant worsening of neurological function (Klineova and Lublin, 2018). After about 15 years, in many affected, patients relapsing form could transition to a progressive clinical course, leading to progressive disability (Cree et al., 2021). A subgroup of relapsing-remitting MS (RRMS) patients who have a more aggressive disease course marked by a rapid accumulation of physical and cognitive deficit, called highly active MS (HAMS), represents approximately 4–15 % of patients from the onset (C Díaz et al., 2019). Risk factors that could help us to identify these patients include demographic, clinical (type of relapse, severity of attacks, frequency of relapses) and imaging characteristics that also provide important prognostic markers both at the onset and during the follow-up of the disease (C Díaz et al., 2019). In the natural course of the disease, there is a "window of opportunity" for effective treatment of RRMS patients. Disease-modifying therapies (DMTs) are most effective when the inflammatory process is prominent, such as in the early stages of the disease (M Filippi et al., 2022). The definition of HAMS includes one or more of the following characteristics: an EDSS scale of 4 points at 5 years from the onset of the disease; multiple relapses (two or more) with incomplete recovery in the ongoing year; more than two brain magnetic resonance imaging (MRI) studies demonstrating new lesions or an increase in the size of the lesions in T2, or lesions that enhance with gadolinium despite treatment; and no response to treatment with one or more DMTs for at least one year (C Díaz et al., 2019). The severity of inflammation in the first few years of the disease causes early disability, which eventually evolves into a chronic neurodegenerative process. Therefore, in HAMS, high activity drugs are required to avoid disability accrual related to multiple relapses. The accumulation of multiple relapses. The goal of treatment is to minimize irreversible disability or halt the progression of the disease. Natalizumab (NAT)and ocrelizumab (OCR) are two monoclonal antibodies considered high efficacy DMTs (HE-DMTs) in disease activity control that act with different mechanism of action. NAT is a recombinant humanized IgG4 monoclonal antibody selective for α4-integrin, controlling and preventing lymphocytes migration across the blood brain barrier (BBB)and acting as sequestering treatment (McCormack, 2013) with a proven efficacy in the AFFIRM and SENTINEL trials (Polman et al., 2006; Rudick et al., 2006). NAT release in the European Union happened in 2006 after a brief stop related to the occurrence of cases of progressive multifocal leukoencephalopathy (PML). PML is an infective and demyelinating central nervous system (CNS) disease, due to the polyomavirus John Cunningham (JCV) reactivation (Baldwin and Hogg, 2013) probably favored by selective immunosuppression in the CNS in high-risk individuals (long duration of treatment and prior use of immunosuppressants), actually mitigated by risk stratification in the individual patient by antibody assay (JCV stratify) and recent use of extended dose (6 weeks instead of 4 weeks timely infusion) (EMA Confirms Recommendations to Minimise Risk of Brain Infection PML with Tysabri; De Mercanti et al., 2021). OCR is a recombinant humanized anti-CD20 mAb approved for the treatment of relapsing forms of MS and primary progressive MS (PPMS) in various countries worldwide (Syed, 2018) approved after demonstrating its efficacy in OPERA I e II trials (Hauser et al., 2017). OCR acts by depleting CD20 lymphocytes, subgroup of lymphocytes (mostly B lymphocytes), particularly implicated in MS immune pathogenesis. In this retrospective study, we will investigate the NEDA-3 achievement in patients with HAMS at first onset of disease treated as first line therapy with NAT or OCR from 2017 (period of OCR release)for at least 3 years. The aim is to compare disease activity (clinical and instrumental) and disability worsening between the two groups after propensity score weighting.

2. Methods

We retrospectively recruited from 14 Italian MS Centers HAMS patients at onset identify by demographic, clinical (type of relapse, severity of attacks, frequency of relapses) and imaging characteristics that also provide important prognostic markers as reported by Diaz et al.: i) EDSS scale of 4 points at 5 years of onset of the disease ii) multiple relapses (two or more) with incomplete recovery in the ongoing year iii) more than 2 brain magnetic resonance imaging (MRI) studies demonstrating new lesions or increase in the size of the lesions in T2, or lesions that enhance with gadolinium but without the response to treatment criteria because were patients naïve to treatment (C Díaz et al., 2019) who started highly efficacy therapy with OCR or NAT within one year from diagnosis of MS and were followed for at least 2 years; we collected data from 2017 (release of OCR in order to reduce selection bias). The study was approved by the local ethics committees and all participants signed an informed consent. The inclusion criteria were: i) HAMS patients who started OCR or NAT as their first therapy within one year from diagnosis, ii) patients with at least 2 years of follow-up in treatment, iii) a dose regimen every 4 weeks for NAT and every six months for OCR without variation in posology during follow up. Patients with a prior diagnosis of progressive MS according to Lorscheider et al. (Lorscheider et al., 2016) were excluded. For each patient we collected the following demographic and clinical information from the patients' data records: year of birth; year of diagnosis; disease duration from onset of disease, disease activity in the year before OCR or NAT defined as annualized relapse rate (ARR) and MRI activity (number of gadolinium enhancing lesions in the last MRI before OCR or NAT start); disease activity after treatment start defined as number of relapses, date of occurred relapse, number of new T2 lesions or gadolinium enhancing lesions accumulated after OCR or NAT treatments. We collected also expanded disability status scale (EDSS) at baseline, after six months and every year of follow up with data of EDSS modification. From clinical (relapse, EDSS) and MRI data we evaluated no evidence of disease activity (NEDA) after one, two and three years of treatments for the two group of patients (cumulative over the follow up). Achievement of NEDA is characterized by no evidence of relapses, no evidence of new T2 lesions or new gadolinium enhancing lesions and no evidence of EDSS disability progression (Rudick et al., 2014).

2.1. Primary objective

The primary outcome was theevaluation of the percentage of patients achieving NEDA-3 at the last follow up in relapsing remitting patients treated with OCR or NAT, followed for at least 2 years.

Among the secondary outcomes the evaluation of the number of pre and post relapses in relapsing remitting MS patients treated with OCR or NAT, the evaluation of the pre and post therapyMRIactivity (in terms of

Table 1
Baseline characteristics.

		Total before IPTW (*N* = 281)	Ocrelizumab before IPTW (*N* = 124)	Natalizumab before IPTW (*N* = 157)	SMD before IPTW	Ocrelizumab after IPTW (*n* = 282.35)	Natalizumab after IPTW (*n* = 280.86)	SMD after IPTW
Age at the start of therapy, years - mean ± SD		32.7 ± 10.33	35.0 ± 10.91	31.0 ± 9.52	0.390	32.8 ± 10.13	32.8 ± 10.35	0.002
Time between MS diagnosis and start of therapy, months – mean ± SD		1.8 ± 2.30	2.1 ± 2.20	1.6 ± 2.36	0.213	1.86 ± 2.01	1.80 ± 2.52	0.027
Sex – n (%)	Female	181 (64.4 %)	77 (62.1 %)	104 (66.2 %)	0.087	185.3 (65.6 %)	183.7 (65.4 %)	0.005
	Male	100 (35.6 %)	47 (37.9 %)	53 (33.8 %)		97.1 (34.4 %)	97.2 (34.6 %)	
Presence of at least one comorbidity – n (%)	No	172 (61.2 %)	80 (64.5 %)	92 (58.6 %)	0.122	169.0 (59.8 %)	169.5 (60.3 %)	0.010
	Yes	109 (38.8 %)	44 (35.5 %)	65 (41.4 %)		113.4 (40.2 %)	111.4 (39.7 %)	
Type of MS onset – n (%)	Not specified	24 (8.5 %)	7 (5.6 %)	17 (10.8 %)	0.248	26.3 (9.3 %)	24.6 (8.8 %)	0.041
	NORB	42 (14.9 %)	20 (16.1 %)	22 (14.0 %)		39.9 (14.1 %)	39.8 (14.2 %)	
	Spinal	70 (24.9 %)	36 (29.0 %)	34 (21.7 %)		67.8 (24.0 %)	69.9 (24.9 %)	
	Brain stem	81 (28.8 %)	34 (27.4 %)	47 (29.9 %)		87.3 (30.9 %)	83.1 (29.6 %)	
	Brain	64 (22.8 %)	27 (21.8 %)	37 (23.6 %)		61.0 (21.6 %)	63.4 (22.6 %)	
EDSS at first DMT - median [IQR]		2.0 (1.5 - 3.0)	2.0 (1.5 - 3.0)	2.5 (1.5 - 3.0)	0.062	2.1 (1.2 – 3.0)	1.9 (1.1 – 3.0)	0.031
Number of relapses in the year prior to diagnosis - mean±SD		1.4 ± 0.77	1.4 ± 0.79	1.5 ± 0.75	0.116	1.4 ± 0.78	1.4 ± 0.77	0.003
Presence of at least one relapse in the year prior to diagnosis – n (%)	No	30 (10.7 %)	15 (12.1 %)	15 (9.6 %)	0.082	30.6 (10.8 %)	30.9 (11.0 %)	0.006
	Yes	251 (89.3 %)	109 (87.9 %)	142 (90.4 %)		251.8 (89.2 %)	250.0 (89.0 %)	
Last MRI pre- treatment: number of GD+ lesion - mean±SD		1.6 ± 2.13	1.6 ± 2.24	1.6 ± 2.04	0.003	1.5 ± 2.07	1.5 ± 2.09	0.005
Last MRI pre- treatment: presence of at least one GD lesion – n (%)	No	99 (35.2 %)	43 (34.7 %)	56 (35.7 %)	0.021	90.7 (32.1 %)	109.7 (38.9 %)	0.143
	Yes	182 (64.8 %)	81 (65.3 %)	101 (64.3 %)		191.7 (67.9 %)	171.2 (61.1 %)	
Last MRI pre-treatment: number of spinal cord lesions - mean±SD		2.4 ± 2.73	3.1 ± 3.06	1.9 ± 2.32	0.424	2.4 ± 2.68	2.4 ± 2.76	0.013
Last MRI pre- treatment: presence of at least one spinal cord lesion – n (%)	No	88 (31.3 %)	29 (23.4 %)	59 (37.6 %)	0.312	83.8 (29.7 %)	89.9 (32.0 %)	0.050
	Yes	193 (68.7 %)	95 (76.6 %)	98 (62.4 %)		198.6 (70.3 %)	191.0 (68.0 %)	

*SMD = standardized mean difference; IPTW = Inverse Probability Treatment Weighting.

new T2 MRI lesions and Gd+ lesions) detected in relapsing remittingMS treated with OCR or NAT, and the evaluation of disability worsening events in terms of an increase of 1 point of EDSS if baseline EDSS was<5.5 or 0.5 point if EDSS at baseline was≥ 5.5.

Further the reasons for discontinuation were assessed.

2.2. Statistical methods

Continuous variables were reported as mean ± standard deviation (SD) or median with interquartile range (IQR), while categorical variables were presented as numbers with percentages.

Standardized mean differences (SMD) between OCR or NAT at baseline were assessed before and after applying an inverse probability of treatment weighting (IPTW) based on the propensity score. The propensity score was calculated through logistic regression, with the treatment group (OCR or NAT) as the dependent variable and the following independent covariates: age, sex, type of onset, time between MS diagnosis and therapy initiation, EDSS score at the start of the first disease-modifying therapy (DMT), the number of relapses in the previous year, and the previous numbers of gadolinium-enhancing (Gd+) lesions and spinal cord lesions.

Differences between groups in time to EDSS progression, time to NEDA-3 loss, and the estimation of the probability of NEDA-3 during the 3 years of observations were evaluated through a IPTW-weighted Kaplan-Meier survival analysis and Log Rank test. The annualized relapse rate (ARR) was calculated using a IPTW-weighted negative binomial regression model, while a binomial logistic regression was applied to evaluate the group effect on MRI activity in the first two years of treatment.

A sensitivity analysis, excluding 6-month re-baseline approach, was conducted to assess any changes in the time to NEDA-3 loss and the probability of NEDA-3 during the 3 years of observations.The data that support the findings of this study are available on request from the authors.R version 4.1.3 (2022–03–10) was used for the computation.

3. Results

3.1. Cohort characteristics

During an observation period of 39.5 months (mean value from re-baseline to the last follow-up),281 naïve relapsing-remitting patients were recruited, with a mean age of 32.7 years (sd 10.33) and 64.4 % were female. The mean number of relapses in the year before the diagnosis was 1.4 (SD 0.77) and the mean number of Gd+ pre-treatment was 1.6 (SD 2.13). In the whole cohort median EDSS at treatment start was 2.0 (IQR: 1.5–3.0) and other demographic and clinical data were resumed in Table 1. The majority of patients had a brain stem or spinal cord onset of pathology and 68.7 % of patients had at least one spinal cord lesion. These described patients, based on clinical practice, started as first treatment OCR or NAT. 124 patients (44.1 %) started OCR and 157 patients (55.9 %) started NAT. Table 1 reports the clinical and demographic characteristics of the two treatment groups after IPTW based on the propensity score, with SMD between the two groups. After IPTW, all covariates were well-balanced between OCR and NAT cohorts.

3.2. NEDA-3

Collecting relapse, MRI lesions (new T2 lesions or Gd+ lesions) and EDSS every year after treatment start, we estimated the probability of reaching NEDA-3 status after one, two and three years of treatment (Table 2). After three years the Kaplan-Meier probability of patients NEDA-3 were 66.0 % (95 %CI: 57.3 % - 76.0 %) with OCR and 68.2 % (95 %CI: 59.9 % - 77.7 %) with NAT. Evaluating time to loss of NEDA-3 with a Kaplan Meier, after re baseline at six months, there were no significant differences between the two treatments ($p = 0.27$) as shown in Fig. 1.In Table 3 and Fig. 2 we resumed cumulative ARR every year

Table 2
Estimation of the probability of NEDA-3.

	Ocrelizumab	Natalizumab
Probability at 1st year	75.1 % (67.1 % - 83.9 %)	79.1 % (72.5 % - 86.3 %)
Probability at 2nd year	68.7 % (60.4 % - 78.2 %)	75.9 % (69.0 % - 83.5 %)
Probability at 3rd year	66.0 % (57.3 % - 76.0 %)	68.2 % (59.9 % - 77.7 %)

over 4 years of follow up without significant differences between groups treated with OCR or NAT. Regarding MRI activity we have not observed any significant differences in terms of the risk of MRI activity in the first two years between treatments (Table 4, $p = 0.08$). Time to disability worsening did not significantly differ between treatments, as shown in Fig. 3 ($p = 0.18$).

A sensitivity analysis, excluding the 6-month re-baseline approach, confirmed the above results and is reported in the Supplementary Material.

3.3. Lost to follow-up and discontinuation

During the study observation period, 10 (3.6 %) patients discontinued the treatment: 1 was on OCR and 9 on NAT. The reasons for discontinuation were as follows: safety reasons (60.0 %), inactivity (1.0 %), patient's non-compliance (1.0 %), pregnancy (1.0 %), and seeking pregnancy (1.0 %). Upon discontinuation, most patients switched to cladribine (40.0 %), while others started fingolimod (1.0 %), ocrelizumab (1.0 %), interferon (1.0 %), or received no new treatment (1.0 %).

Among them, the only patient on OCR discontinued the treatment

Table 3
Cumulative ARR.

	Ocrelizumab	Natalizumab	p
1 year	0.025 (0.008 – 0.077)	0.006 (0.001 – 0.046)	0.99
2 years	0.013 (0.004 – 0.042)	0.014 (0.005 – 0.036)	0.29
3 years	0.014 (0.005 – 0.038)	0.012 (0.005 – 0.030)	0.33
4 years	0.013 (0.005 – 0.036)	0.014 (0.007 – 0.031)	0.21

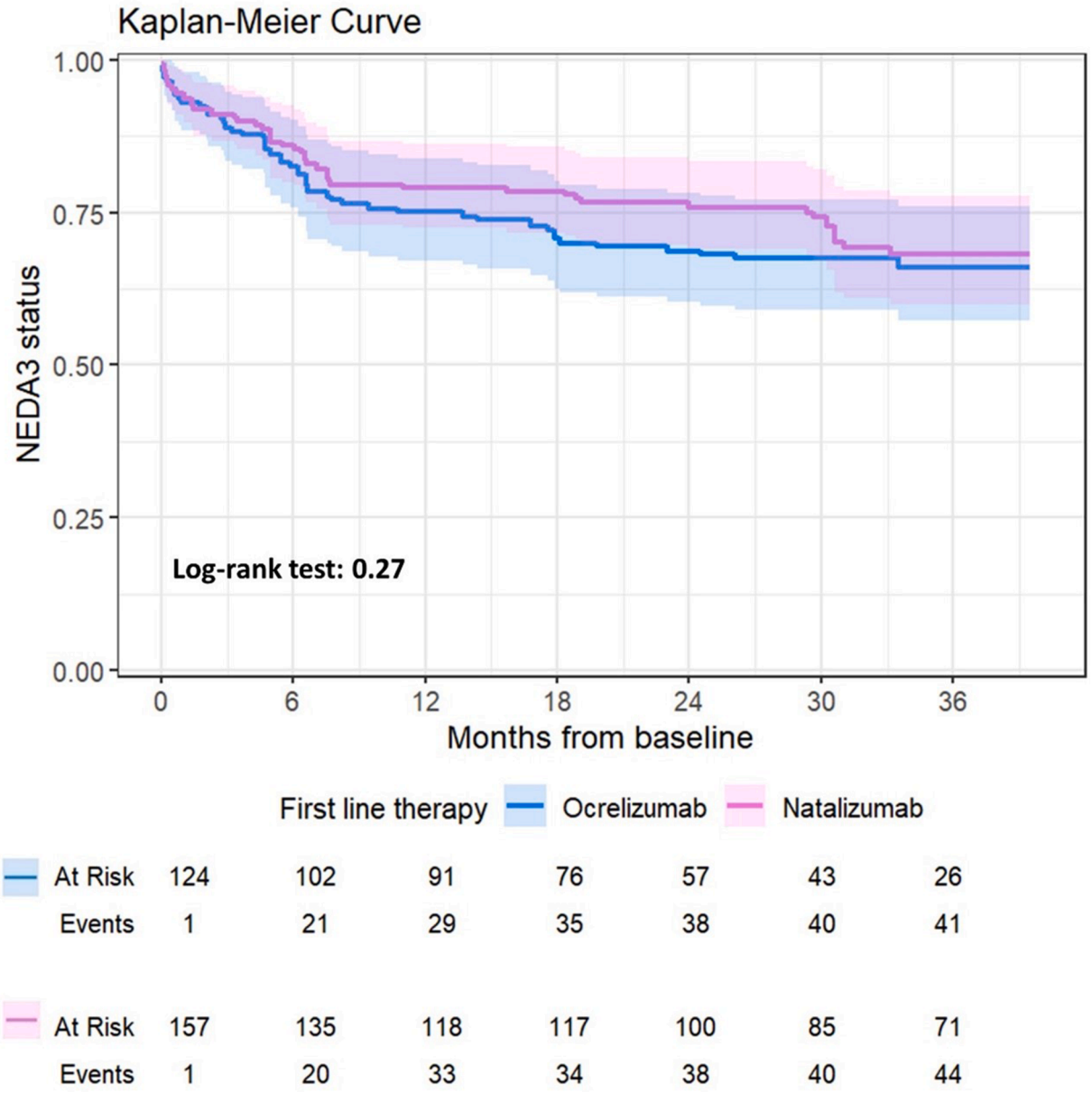

Fig. 1. Time to NEDA-3 loss.

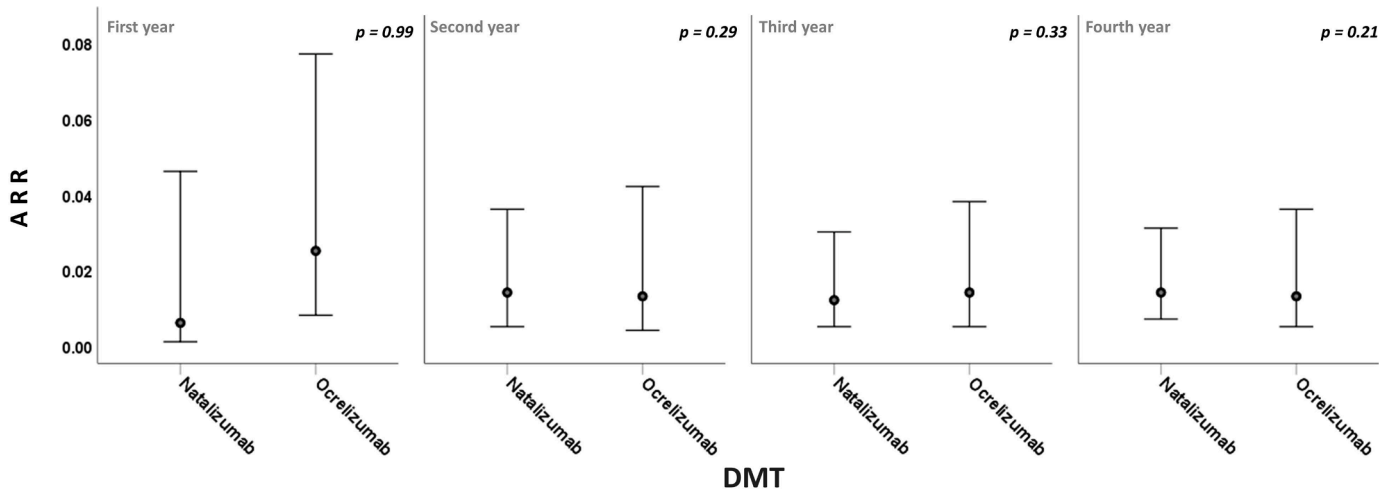

Fig. 2. ARR during the observation period.

Table 4
Group effect on MRI activity in the first two years of treatment.

	Absent	Present	OR (95 %CI), p
Ocrelizumab	95 (76.6 %)	29 (23.4 %)	OR 0.57 (0.31 - 1.06); $p = 0.08$
Natalizumab	128 (81.5 %)	29 (18.5 %)	

OR = odds ratio; CI = confidence interval.

due to seeking pregnancy and switched to interferon.

For all these patients, the date of discontinuation was considered as the last follow-up.

A 23-year-old female patient was lost to follow-up at 85 months of observation.

EDSS progression

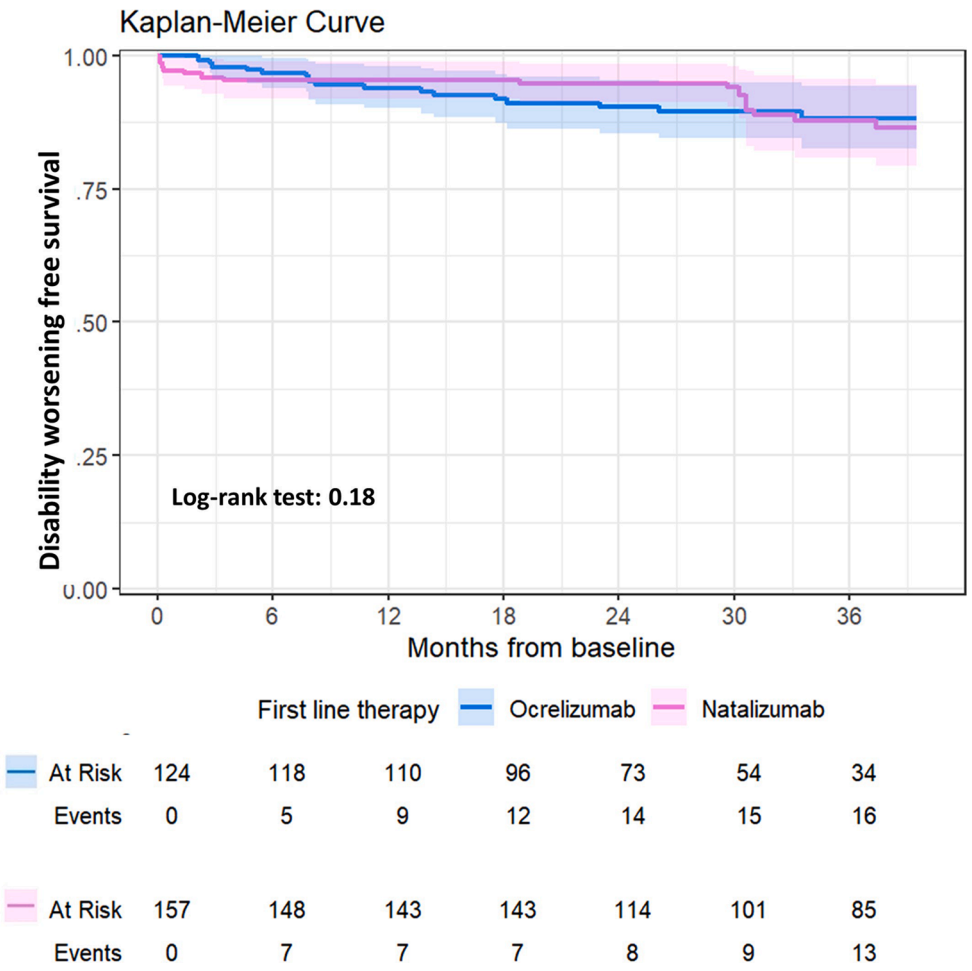

Fig. 3. Time to disability worsening.

3.4. Discussion and conclusions

Here we investigate the probability of reaching NEDA-3 in early, naïve, highly active RR-MS patients treated with high-efficacy therapies such as OCR or NAT.

As an expert opinion affirm, high efficacy treatments can reduce the annualized relapse rate by 50 % and MRI activity by 70 % (M Filippi et al., 2022); for this reason, OCR and NAT were considered high efficacy treatments, as confirmed in clinical trials and network metanalysis (Giovannoni et al., 2020). Over the past few years, there has been much discussion about what may be the best therapeutic strategy to use in patients diagnosed with MS, either an escalation strategy (starting with low-to-medium efficacy drugs and eventually moving to high efficacy therapies in case of therapeutic failure), or an induction strategy, i.e., starting with highly effective therapies that can modify the course and could have long lasting efficacy. Although, to date, apart from off-label immunosuppressive therapies (mitoxantrone or cyclophosphamide) the only inductive therapies are cladribine or alemtuzumab (Freedman, 2018). This is why today we talk about early intensive treatment rather than induction, by having available drugs with high efficacy but no inductive effects. Several studies showed that starting early intensive treatment in the naïve patient from disease onset could reduce disability progression at 5 and 10 years compared with an escalation strategy (Iaffaldano et al., 2021), and it would be easier to achieve therapeutic goals such as NEDA-3 (Giovannoni, 2018). Here we demonstrate that starting an early intensive treatment as NAT or OCR give us a high probability of achieving NEDA-3 at three years in 66 % of OCR-treated patients and 68.2 % of NAT-treated patients without significant differences between treatments. This is in line with another study that investigated the effectiveness and treatment continuation of NAT and OCR in a real-world cohort of German patients (Pape et al., 2022). In this study, with a smaller sample of patients and including patients not treatment naive, NEDA-3 after 30 months of follow-up was reached by 53.1 % in the OCR group and 36.1 % in the NAT group ($p = 0.177$) but OCR was superior to NAT concerning the occurrence of relapses. The lower probability after 30 months to achieve NEDA −3 in this population could be affected by switchers populations and by a higher EDSS at baseline in particular for OCR patients that discontinued treatment for occurrence of secondary progression in the majority of the cases. Further in the population were included also patients switching from NAT to OCR. In this study, we registered a lower percentage of discontinuation from treatment; the majority of patients withdrawal treatment with NAT for safety reason or seeking pregnancy. Our results confirmed that starting in highly active naïve patients with HE-DMTs give us higher chance to control the disease achieving NEDA-3. This endpoint has been proven to be an excellent surrogate for long-term disability (Pape et al., 2022) and is associated with no long-term disability progression in RRMS on both low and high efficacy therapies. The main limit of this study relies on its retrospective, real-world design. but the results should be confirmed by randomized trials.

In conclusion, we demonstrated a similar and long lasting effectiveness of NAT or OCR to achieve NEDA −3 in highly active naïve MS patients. After three years of follow up, the probability was 66 % for OCR and 68 % for NAT, identifying the best population of patients targeting HE-DMTs.

CRediT authorship contribution statement

Elisabetta Signoriello: Writing – review & editing, Writing – original draft, Validation, Supervision, Investigation, Data curation, Conceptualization. **Alessio Signori:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization. **Giacomo Lus:** Data curation, Investigation. **Giuseppe Romano:** Data curation, Investigation. **Girolama Alessandra Marfia:** Data curation, Investigation. **Doriana Landi:** Data curation, Investigation. **Francesca Napoli:** Data curation, Investigation. **Emanuele D'Amico:** Data curation, Investigation. **Aurora Zanghí:** Data curation, Investigation. **Paola Sofia Di Filippo:** Data curation, Investigation. **Daniele Caliendo:** Data curation, Investigation. **Antonio Carotenuto:** Data curation, Investigation. **Antonio Luca Spiezia:** Investigation, Data curation. **Roberta Fantozzi:** Investigation, Data curation. **Diego Centonze:** Investigation, Data curation. **Matteo Lucchini:** Investigation, Data curation. **Massimiliano Mirabella:** Investigation, Data curation. **Eleonora Cocco:** Investigation, Data curation. **Jessica Frau:** Investigation, Data curation. **Giorgia Teresa Maniscalco:** Investigation, Data curation. **Maria Elena Di Battista:** Investigation, Data curation. **Matteo Foschi:** Investigation, Data curation. **Andrea Surcinelli:** Investigation, Data curation. **Simona Bonavita:** Investigation, Data curation. **Gianmarco Abbadessa:** Investigation, Data curation. **Livia Pasquali:** Investigation, Data curation. **Maria Di Gregorio:** Investigation, Data curation. **Maria Teresa Ferrò:** Data curation, Investigation. **Maria Pia Sormani:** Methodology. **Irene Schiavetti:** Conceptualization, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Irene Schiavetti reports a relationship with Roche, Biogen, Horizon, Novartis, Hoya, Hippocrates Research, D.M.G Italia, Eyepharma, DreamsLab that includes: consulting or advisory. Livia Pasquali reports a relationship with Alexion, Biogen, Sanofi, Merck, Novartis, Roche that includes: consulting or advisory and travel reimbursement. Elisabetta Signoriello reports a relationship with Almirall, Biogen, Genzyme, Novartis, Teva that includes: board membership and travel reimbursement. Maria Pia Sormani reports a relationship with Biogen Idec, Merck Serono, Teva, Genzyme, Roche, Novartis, GeNeuro, Medday that includes: consulting or advisory. Jessica Frau reports a relationship with Biogen, Bristol, Novartis, Genzyme, Merck, Teva, Alexion that includes: board membership, consulting or advisory, and speaking and lecture fees. Daniele Caliendo reports a relationship with Merck that includes: funding grants. Alessio Signori reports a relationship with Roche, Horizon, Novartis that includes: speaking and lecture fees. Andrea Surcinelli reports a relationship with Roche, Merck, Biogen, Sanofi, Novartis that includes: travel reimbursement. Simona Bonavita reports a relationship with Novartis, Merck-Serono, Alexion, BMS, Biogen, Roche, Janssen-Cilag, Horizon that includes: speaking and lecture fees and travel reimbursement. Roberta Fantozzi reports a relationship with Novartis, Roche, Merck Serono, Bristol-Myers Squibb that includes: board membership and consulting or advisory. Antonio Carotenuto reports a relationship with Almirall, ECTRIMS- MAGNIMS, Biogen, Roche, Sanofi-Genzyme, Merck, Ipsen, Novartis that includes: funding grants. Doriana Landi reports a relationship with Biogen, Merck Serono, Teva, Bristol Myers Squibb, Mylan, Novartis, Roche, Horizon, Alexion, Sanofi-Genzyme, Novartis, Bayer-Schering that includes: speaking and lecture fees and travel reimbursement. Giacomo Lus reports a relationship with Biogen Idec, Merck Serono, Novartis, Sanofi- Aventis Pharmaceuticals, Teva neuroscience that includes: funding grants. Eleonora Cocco reports a relationship with Biogen, Merck, Novartis, Roche, Genzyme that includes: consulting or advisory and funding grants. Matteo Lucchini reports a relationship with Biogen, Merck Serono, Novartis, Roche, Sanofi-Genzyme, Almirall, Horizon, Bayer that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Girolama Alessandra Marfia reports a relationship with Almirall, Bayer-Schering, Biogen, Sanofi Genzyme, Merck Serono, Novartis, Teva, Mylan, Bristol Mayers Squibb, Roche, Biogen that includes: consulting or advisory, funding grants, speaking and lecture fees, and travel reimbursement. Matteo Foschi reports a relationship with Merck, Biogen, Sanofi, Roche, Novartis that includes: consulting or advisory and travel reimbursement. Massimiliano Mirabella reports a relationship with Bayer Schering, Biogen, Sanofi-Genzyme, Merck, Novartis, Teva, Mylan, Almirall, CSL

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2024.105594.

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