SWITCH TO NATALIZUMAB OR FINGOLIMOD IN PATIENTS WITH ACTIVE MULTIPLE SCLEROSIS WHO FAILED FIRST-LINE THERAPIES: AN OBSERVATIONAL, BICENTER, COMPARISON STUDY

D. Baroncini[1], A. Ghezzi[1], P.O. Annovazzi[1], M. Zaffaroni[1], V. Martinelli[2], B. Colombo[2], L. Moiola[2], M. Rodegher[2], G. Minonzio[3], M.J. Messina[2], M. Romeo[2], F. Sangalli[2] and G. Comi[4]

[1]Multiple Sclerosis Study Center, Sant'Antonio Abate Hospital, Gallarate, Italy; [2]Department of Neurology, San Raffaele Hospital, Milan, Italy; [3]Neuroradiology Department, Sant'Antonio Abate Hospital, Gallarate, Italy; [4]Department of Neurology, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Hospital, Milan, Italy

Background

In Europe both natalizumab (NAT) and fingolimod (FTY) have been approved by European Medicines Agency (EMA) as second-line treatments for relapsing remitting multiple sclerosis (RRMS) not responding to first-line agents (i.e. interferons [IFNs], glatiramer acetate [GA]) or with a rapidly evolving course at onset [1, 2]. These indications were based on results of randomized clinical trials (RCTs), in which both NAT and FTY strongly lowered clinical and brain MRI activity respect to placebo and IFNb-1a [3-7].

So far there are no available data of randomized head-to-head studies comparing NAT vs FTY. However, different groups tried to make an indirect comparison of the clinical efficacy between these two drugs, with divergent findings. For examples, a first, observational, cohort study performed in Germany using data routinely collected in outpatient neurology practices did not find any significant differences between the two agents [8]. Conversely, in a large international, multicentre, cohort study using data from MSBase it was found a superiority of NAT over FTY for relapses control and disability regression [9].

Objectives

To compare clinical (relapses, disability worsening and improvement) and MRI (presence of activity, number of new/enlarged T2 and Gd+ lesions) effectiveness of NAT versus FTY in a real life, intention-to-treat (ITT) cohort study of Italian RRMS patients who failed to respond to first line treatments (i.e. IFNs and GA).

Methods

INCLUSION CRITERIA

- All consecutive patients with active RRMS who started FTY or NAT from June 2011 to February 2014 in two Italian MS centers (Sant'Antonio Abate Hospital and San Raffaele Hospital);
- Age ≥ 18 years old;
- Failure to respond to first line DMDs (IFNs or GA) according to EMA criteria in the precedent year;

EXCLUSION CRITERIA

- Treatment with immunosuppressors (ISs) in the year before FTY/NAT initiation. A precedent treatment with ISs was otherwise allowed;
- Progressive MS without a clear inflammatory activity;
- Previous treatment with FTY and/or NAT;

DATA COLLECTION

We retrospectively reviewed prospectively collected demographic and clinical data from electronic databases (iMED), and from paper/electronic documents. Neurological examination and EDSS assessment was performed monthly for NAT cohort, quarterly for FTY cohort. The last brain MRI scan performed in the previous year before NAT/FTY initiation was considered the baseline. Subsequent brain MRI scan were planned yearly for FTY patients, every six months for NAT patients. Spinal cord MRI scan were not counted. Due to the study's observational design, brain MRI scans were not done in the same center, and different acquisition protocols were used. Anti-JCV antibodies status was determined by STRATIFY JCV Antibody ELISA test at baseline in all NAT treated patients, then every 6 months for negative/low index patients. Patients lost to follow-up were considered reactivated for every outcomes, according to the "worst case" scenario analysis.

OUTCOME MEASURES

- **Clinical relapse:** new or worsening neurologic symptoms with at least 24 hours of duration based on history and neurological examination, in the absence of fever and infections. Annualized relapse rate (ARR) was calculated in each subject;
- **Brain MRI activity:** presence of ≥1 new/enlarging T2 lesion respect to previous brain MRI and/or the presence of ≥1 Gd+ lesion;
- **Disability worsening**: EDSS score increase of ≥1 point (≥1.5 points if baseline EDSS=0, and ≥0.5 points if baseline EDSS=5.5), confirmed after 6 months;
- **Disability improvement:** EDSS score decrease of ≥1 point (baseline EDSS should be ≥ 1.5), confirmed after 6 months;
- **No evidence of disease activity (NEDA-3):** absence of relapses, brain MRI activity and disability worsening as previously described (patients without at least 1 brain MRI scan yearly were excluded for NEDA-3 assessment);

PROPENSITY SCORE MATCHING

Propensity score (PS) and gender 1:1 exact matching method was used.

Covariates used for PS estimation: age, MS center, MS duration, time between MS onset and first treatment, type and duration of previous first line agents, use of ISs, ARR in previous 2/1 years, brain MRI activity and number of new/enlarging T2 lesions and Gd+ lesions at baseline, baseline EDSS score, absolute difference of baseline EDSS score – 1/2 years earlier EDSS score.

STATISTICS

Survival times outcomes were compared first using a Log rank test, then using a multivariate model (Cox's proportional hazards) adjusted for all covariates used for PS estimation, gender and wash-out period between first-line agents and FTY/NAT initiation. Hazard ratios (HR) and relative CI 95% were estimated. Continuous outcomes (e.g. ARR) were compared using Mann-Whitney test, nominal variables using Chi-Square test. All analysis were performed in the ITT population. A significance level of 0.05 was used for each test. SPSS IBM v. 21 program was used.

Results

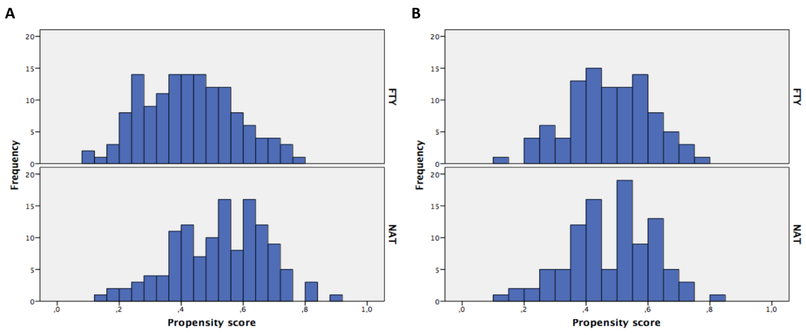

Figure 1. PS distribution in NAT and FTY cohort before (A) and after (B) pair-matching. The logistic model used to estimate PS found a higher probability of switching to NAT therapy in patients with a higher EDSS score (OR 1.21, p=0.05) and more Gd+ lesions (OR 1.29, p=0.022) at baseline. Conversely, previous use of ISs (OR 0.28, p=0.014) and lower age (OR 0.97, p=0.028) were negatively correlated to NAT initiation.

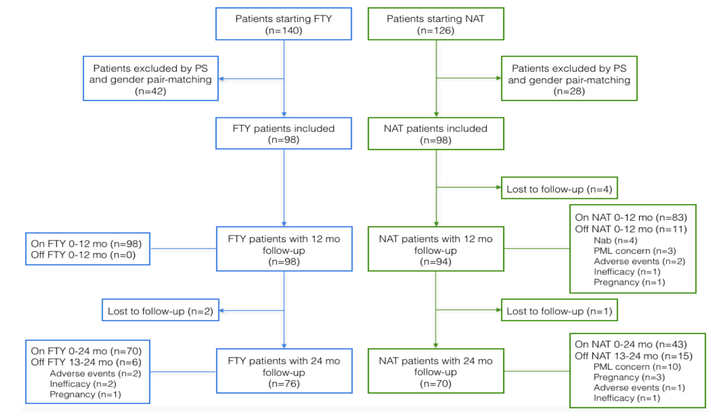

Figure 2. Enrollment, inclusion, and follow-up of study population. mo, months.

Baseline characteristics	FTY (98 pts)	NAT (98 pts)	p
MS center (H. Gallarate/H. San Raffaele)	40/58	41/57	0.885
Females (%)	71 (72%)	71 (72%)	1.000
Age (y), mean±SD	38.7±9.1	37.7±9.3	0.443
Disease duration (y), mean±SD	11.1±7.5	10.6±6.5	0.851
Patients with previous use of ISs (%)	12 (12%)	9 (9%)	0.488
Previous DMDs duration (y), mean±SD	5.7±3.9	5.7±3.8	0.922
Type of DMDs used (IFNs/GA/both)	47/17/34	46/18/34	0.981
Washout period (m), mean±SD	1.2±1.7	1.3±1.6	0.411
ARR 1y pre, mean±SD	1.2±0.5	1.2±0.7	0.250
Patients with an active brain MRI scan (%)	72 (73%)	76 (78%)	0.506
New/enlarged T2 lesions, mean±SD	1.5±1.5	1.7±1.7	0.342
Gd+ lesions, mean±SD	0.8±1.2	0.9±1.2	0.342
EDSS score at baseline, mean±SD	2.3±1.2	2.1±1.2	0.149
2y EDSS score worsening ≥ 1 point (%)	37 (38%)	38 (39%)	0.768

Table 1. Baseline clinical and demographic characteristics of FTY and NAT matched cohorts. SD, standard deviation. mo, months. y, years. IFNs, interferons. GA, glatiramer acetate. DMDs, first-line disease modyfing drugs. ISs, immunosoppressors.

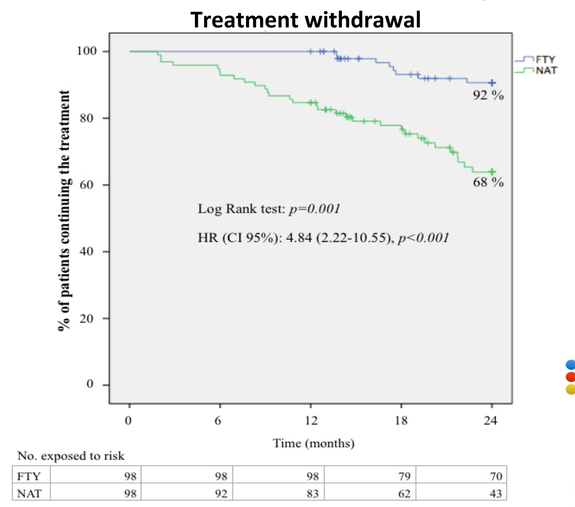

Figure 3. Kaplan-Meier survival estimates for time to withdrawal of FTY/NAT. HR, Hazard ratio. CI, confidence interval. No significant predictive variables of FTY therapy interruption were found. Predictors of NAT withdrawal were JCV positive status (HR 4.10, p=0.013) and disease duration (HR 2.35, p=0.044).

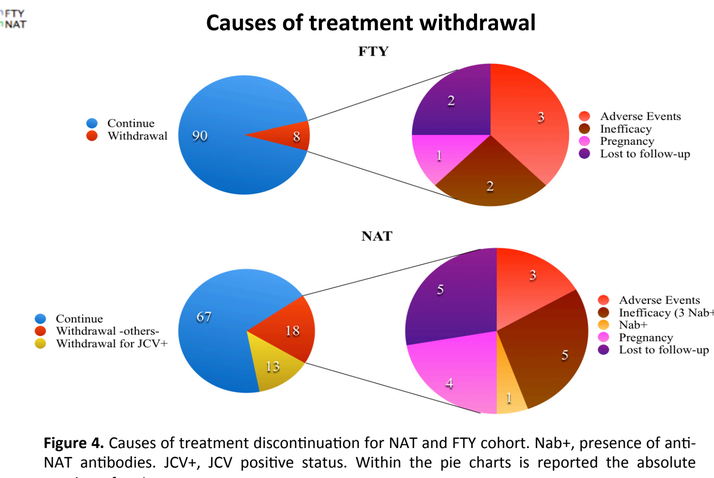

Figure 4. Causes of treatment discontinuation for NAT and FTY cohort. Nab+, presence of anti-NAT antibodies. JCV+, JCV positive status. Within the pie charts is reported the absolute number of patients.

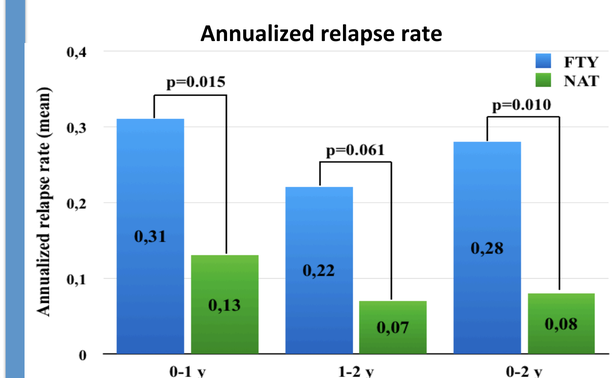

Figure 5. Comparison of mean ARR between NAT and FTY cohorts. y, year. p values estimated with Mann-Whitney test.

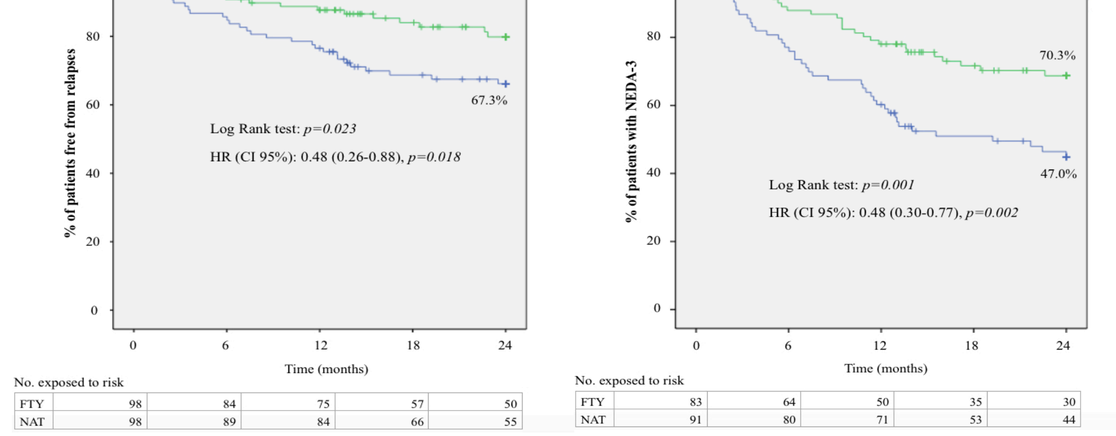

Figure 6. Kaplan-Meier survival estimates for time to first relapse. HR, Hazard ratio. CI, confidence interval. No., number. It is shown HR of adjusted analysis. Additional independent predictors of relapses were: activity at baseline brain MRI (HR 2.72, p=0.018), baseline EDSS score (HR 1.74, p=0.001), no. Gd+ lesions at baseline brain MRI (HR 1.55, p=0.009).

Figure 7. Kaplan-Meier survival estimates for the time to first evidence of disease activity. HR, Hazard ratio. CI, confidence interval. No., number. It is shown HR of adjusted analysis. Additional independent predictor of disease activity was baseline EDSS score (HR 1.34, p=0.026). Patients who did not perform a brain MRI scan yearly (n=7 for NAT; n=15 for FTY) were excluded from the analysis.

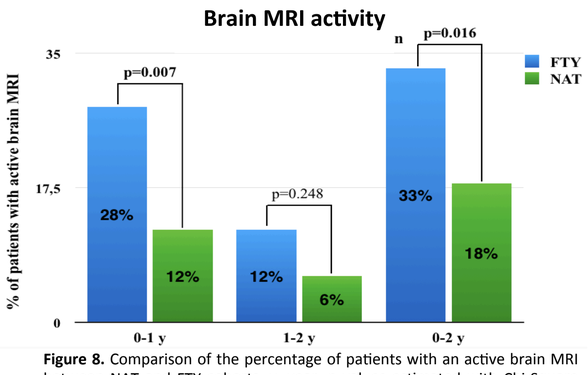

Figure 8. Comparison of the percentage of patients with an active brain MRI between NAT and FTY cohorts. y, year. p values estimated with Chi-Square test. Patients who did not perform a brain MRI scan yearly (n=7 for NAT; n=15 for FTY) were excluded.

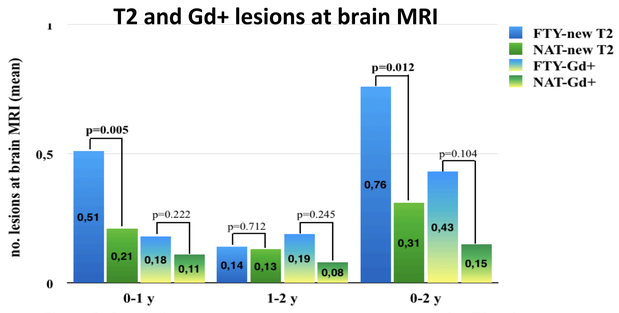

Figure 9. Comparison of mean number (no.) of new/enlarging T2 lesions (new T2), and of Gd+ lesions at brain MRI between NAT and FTY cohorts. y, year. p values estimated with Mann-Whitney test. Patients who did not perform brain MRI scan yearly (n=7 for NAT; n=15 for FTY) were excluded.

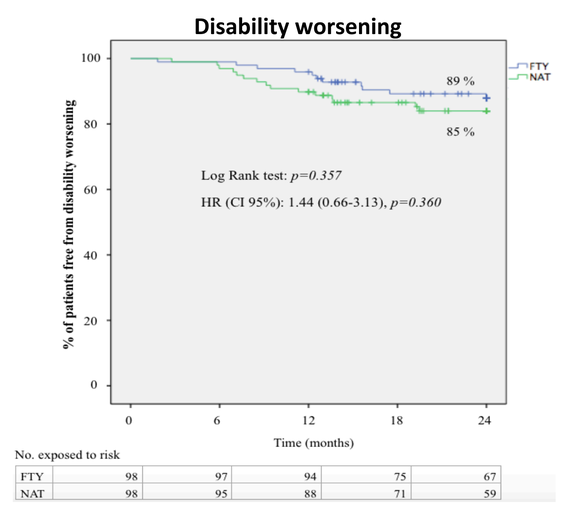

Figure 10. Kaplan-Meier survival estimates for time to disability worsening. HR, Hazard ratio. CI, confidence interval. No., number. It is shown HR of adjusted analysis. Additional independent predictors of disability worsening were baseline EDSS score (HR 3.14, p<0.001), previous DMDs duration (HR 0.85, p=0.043) and disease duration (HR 1.07, p=0.042).

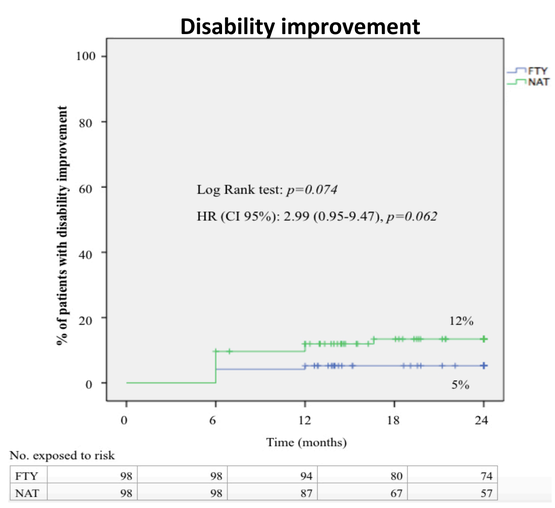

Figure 11. Kaplan-Meier survival estimates for time to disability improvement. HR, Hazard ratio. CI, confidence interval. No., number. It is shown HR of adjusted analysis. Additional independent predictor of disability improvement was the absolute difference of baseline – 1 year earlier EDSS score (HR 6.19, p=0.016).

Discussion and conclusion

In our study NAT was twice superior to FTY treatment in reducing relapse occurrences and disease activity (according to NEDA-3 status) in RRMS patients non-responding to injectable first-line agents. A significant reduction in ARR and MRI outcomes was observed during the first year, while in the second year the differences did not reach statistical significance. The effect of NAT and FTY treatment on disability worsening was similar after 2 years. Compared to FTY, NAT treatment could lead to a faster improvement of EDSS score in patients with a higher and recent accumulation of disability. These results are in line with those of Kalincik et al [9].

In considering a valuable therapy after first-line failure is therefore mandatory to take into account on one hand the faster and higher reduction of clinical and MRI disease activity with NAT treatment, on the other hand safety issues concerning PML, which led to a much higher discontinuation rate in NAT cohort with respect to FTY cohort. The risk of reactivation after NAT withdrawal is another important problem to deal with. Bearing in mind these considerations, evaluating disease activity, stratifying PML risk and assessing patients risk propensity should guide the choice of second-line treatment.

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