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Abstract

In this independent, multicentre post-marketing study we directly compared the effectiveness of natalizumab (NTZ), fingolimod (FNG) and self-injectable drugs (INJ), in non-responders to first immunomodulating treatment and in highly active treatment-naïve patients with multiple sclerosis. As

main outcome measure we considered the proportions of patients with no evidence of disease activity (NEDA-3), defined as absence of relapses, disability worsening and radiological activity. A total of 567 non-responders to interferon beta (IFNB) or glatiramer acetate (GA) [dataset A] and 216 highly active treatment-naïves [dataset B] were followed up to 24 months from the beginning of NTZ, FNG or INJ, i.e. switching from IFNB to GA or viceversa (in the case of non-responders) or starting high-dose IFNB (in the case of highly active treatment-naives). Propensity score matching in a 1:1:1 ratio was used to select only patients with similar baseline characteristics, retaining 330 and 120 patients in dataset A and B, respectively. In dataset A, the 24-month proportion with NEDA-3 was greater in both NTZ group (67%) and FNG group (42%) than in INJ group (35%) ($p \leq 0.016$); however, NTZ was superior to FNG in promoting the attainment of NEDA-3 status ($p = 0.034$). In dataset B, the 24-month proportion with NEDA-3 was greater in NTZ group (75%) and FNG group (67%) than in INJ group (40%), but the small cohort sizes most likely prevented the detection of any statistically significant difference. Our study provides real-world evidence that NTZ was more effective than both FNG and INJ in non-responders, while it could seem that, in highly active treatment-naives, NTZ was as effective as FNG and both were superior to INJ.

Keywords (separated by '-') Multiple sclerosis - Propensity score - NEDA - Disease-modifying drugs

Footnote Information **Electronic supplementary material** The online version of this article (doi:10.1007/s00415-016-8343-5) contains supplementary material, which is available to authorized users.

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ORIGINAL COMMUNICATION

Real-world effectiveness of natalizumab and fingolimod compared with self-injectable drugs in non-responders and in treatment-naive patients with multiple sclerosis

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Abstract In this independent, multicentre post-marketing study we directly compared the effectiveness of natalizumab (NTZ), fingolimod (FNG) and self-injectable drugs (INJ), in non-responders to first immunomodulating treatment and in highly active treatment-naïve patients with multiple sclerosis. As main outcome measure we considered the proportions of patients with no evidence of disease activity (NEDA-3), defined as absence of relapses, disability worsening and radiological activity. A total of 567 non-responders to interferon beta (IFNB) or glatiramer acetate (GA) [dataset A] and 216 highly active treatment-naïves [dataset B] were followed up to 24 months from the beginning of NTZ, FNG or INJ, i.e. switching from IFNB to GA or viceversa (in the case of non-responders) or starting high-dose IFNB (in the case of highly active treatment-naives). Propensity score matching in a 1:1:1 ratio was used to select only patients with similar baseline characteristics, retaining 330 and 120 patients in dataset A and B, respectively. In dataset A, the 24-month proportion with NEDA-3 was greater in both NTZ group (67%) and FNG group (42%) than in INJ group (35%) ($p \leq 0.016$);

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however, NTZ was superior to FNG in promoting the attainment of NEDA-3 status ($p = 0.034$). In dataset B, the 24-month proportion with NEDA-3 was greater in NTZ group (75%) and FNG group (67%) than in INJ group (40%), but the small cohort sizes most likely prevented the detection of any statistically significant difference. Our study provides real-world evidence that NTZ was more effective than both FNG and INJ in non-responders, while it could seem that, in highly active treatment-naives, NTZ was as effective as FNG and both were superior to INJ.

Keywords Multiple sclerosis · Propensity score · NEDA · Disease-modifying drugs

Introduction

Despite the increased availability of disease-modifying drugs (DMDs) for treating relapsing-remitting multiple sclerosis (RR-MS), there is not yet evidence-based algorithm to drive specific decision-making about which is the optimal treatment approach for non-responders to self-injectable interferon beta (IFNB) and glatiramer acetate (GA) [1].

A "lateral" switch approach—i.e. changing treatment from low-dose/frequency to high-dose/frequency IFNB, or from IFNB to GA, or viceversa—is a commonly adopted strategy in case of treatment failure or intolerability. However, studies exploring the effectiveness of lateral switch had different designs and provided conflicting results [2–5].

An "escalation" approach—i.e. stepping up from a self-injectable DMD to a more aggressive treatment with less favorable risk:benefit ratio—has been reported to be more effective than lateral switch in patients who did not respond to IFNB or GA [6–9]. However, post-marketing studies aimed to explore which escalation strategy (NTZ or FNG) is more effective in non-responders provided mixed results [10–14]. However, these inconsistencies may be attributable to the heterogeneous treatment effectiveness in different treatment scenarios [15].

Optimal treatment strategies have yet to be defined even in highly active treatment-naïve patients with MS, where there are no data comparing the effectiveness of NTZ and FNG.

Therefore, in this study we sought to explore the effectiveness of NTZ, FNG and first-line injectable DMDs in two different datasets of patients, i.e. non-responders to first-line therapy and highly active treatment-naïve patients.

Methods

Study design

This was an independent, multi-centre, post-marketing study. We retrospectively analyzed data of patients affected by RR-MS and regularly attending eight tertiary MS Centres in Italy. Clinical and magnetic resonance imaging (MRI) data were prospectively collected and stored into an electronic database after approval by ethical committees and after obtaining an informed consent by each participant.

This study was conducted in accordance with specific national laws and the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. In no way this study did interfere in the care received by patients.

Participants

We considered two different patients' datasets:

1. Non-responders (dataset A): patients who experienced either ≥2 relapses or 1 relapse associated with a residual Expanded Disability Status Scale (EDSS) score ≥2.0 in the previous year while on GA or IFNB, and, therefore, were submitted to start NTZ or FNG according to the Italian regulatory criteria [16]. We also included a group of patients who met the same criterion, but were switched from IFNB to GA or viceversa (INJ) because of patient preference's or unavailability of an DMDs. Patients with previous exposure to immunosuppressive drugs were not considered for this study.
2. Highly active treatment-naïves (dataset B): patients who had never been treated before with any DMD and had experienced ≥2 relapse in the previous year and

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≥1 gadolinium (GD)-enhancing lesion on brain or spinal cord MRI scan. These patients were submitted to start NTZ or FNG as first treatment according to the Italian regulatory criteria [16]. We also included a group of patients who met the same criterion, but started high-dose, high-frequency IFNB-1b or 1a (INJ) because of patient preference's or unavailability of an alternative DMDs.

Assessments

All patients were followed for a 24-month observation period. Clinical visits were scheduled at least every 6 months and included disability scoring by means of the EDSS. Each patient underwent brain and spinal cord MRI scan at baseline (within 30 days before DMD starting) and at least every 6 months according to standardized procedures using 1.5 Tesla magnets [17]. Scans were performed before and after GD-DTPA injection, focusing on the presence of radiological activity, i.e. GD-enhancement on T1-weighted images, or the occurence of new hyperintense lesions on T2-weighted images when compared to the baseline scan.

Both pre-planned clinical examinations and MRI scans were collected after 1 month of clinical stability and at least 30 days after the last assumption of steroids. Unscheduled visits and/or MRI scans were also performed in case of relapse or any other clinically relevant condition, including adverse events.

Outcome measure definition

As primary outcome, we estimated the proportions of patients who had "no evidence of disease activity" (NEDA-3), a combined measure defined as absence of clinical relapses, disability worsening, and radiological activity [18]. NEDA has been recently proposed as a principal aim in management of RR-MS because it leads to better long-term outcomes [19, 20].

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

A relapse was defined as any new neurological symptom, not associated with fever or infection, lasting for at least 24 h and accompanied by new neurological signs.

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 [21].

Radiological activity was defined as the occurence of ≥1 GD-enhancing lesion or ≥1 new T2-hyperintense lesions. We decided to not consider enlarging T2-hyperintense lesions since a previous study demonstrated a poor between-rater agreement for this metric under routine clinical setting [22].

The occurrence of disability reduction, defined as a 6-month sustained decrease of ≥1-EDSS point confirmed at the end of the 24-month follow-up, was also explored as tertiary outcome [23].

Patients whose disability worsening or reduction started over the last few months of the pre-planned observational period had an additional follow-up to confirm the outcome reach.

Statistical analysis

All values were expressed as mean (SD) for continuous variables and as count (proportion) for categorical variables.

For dataset A, we considered the following data at baseline (i.e. at DMD change after GA or IFNB failure) data: sex, age, time since first symptom, EDSS score, relapses in the previous year, absence/presence of GD-enhancement.

For dataset B, we considered the following data at baseline (i.e. at treatment start): sex, age, time since first symptom, relapses in the previous year, EDSS score. In this latter dataset we did not include data on the baseline MRI scan since all patients had ≥1 GD-enhancing lesion as per eligibility criteria (see above).

Between-group differences in baseline characteristics were tested using the Chi squared or the Kruskall-Wallis H tests, as appropriate, with Dunn's post-hoc tests for pairwise comparisons.

Primary and secondary outcomes were formerly explored by unadjusted comparisons between the three groups using the Chi squared test.

Since patients in both datasets were not randomized to treatment group, we performed a 1:1:1 ratio propensity score (PS)-based nearest neighbor matching procedure within a calliper of 0.05 and 0.1 for dataset A and B, respectively, without replacement [24]. According to the common-referent approach, two separate PS were derived using multivariable logistic regressions to estimate the conditional probability to receive NTZ vs. INJ and FNG vs. INJ, respectively; we then matched pairs of subjects with overlapping PS in NTZ and FNG groups [25]. The validity of PS matching was tested by analysis of standardized differences (|d|), with $|d| > 0.20$ considered as imbalance [26].

Primary, secondary and tertiary outcomes were then explored in matched samples by Cox proportional hazard regression models, adjusted for sex and age and stratified by matched cases [27]. As main time variable we used the

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length of the observation (in months) between the baseline and the last visit over the 24-month period, or outcome reach, whichever came first.

Post-estimation sensitivity analyzes were applied to primary outcome in both datasets to test the sensitivity of the matched models to an hypothetical confounder that was either not collected or incompletely observed [28, 29].

All two-tailed p values <0.05 were considered as significant after correction for multiple comparison using the Bonferroni–Holm procedure. Data were analyzed using the Statistical Package for Social Sciences, version 16.0 (IBM SPSS, Inc., Chicago, Ill., USA).

Results

Dataset A

Participants We collected data from 567 patients who did not respond to GA or IFNB ($n = 215$ and $n = 352$, respectively) after at least 12 months of continuous treatment. Of them, 150 were switched to the alternative self-injectable DMD type, 202 started FNG, and 215 started NTZ (Fig. 1). Unadjusted comparisons of effectiveness among the three different DMDs showed that: (1) NTZ was superior to INJ in all outcomes ($p < 0.01$); (2) FNG was superior to INJ in all outcomes ($p \leq 0.01$), except one (disability reduction, $p = 0.2$); (3) NTZ was superior to FNG in achieving NEDA-3, suppressing radiological activity and promoting disability reduction ($p < 0.05$), but there was no difference in terms of relapses and disability worsening (p values >0.1).

We observed significant imbalance in pre-matching baseline characteristics across treatment groups (Table 1). Post-hoc tests indicated that patients escalated to NTZ were younger and had more relapses in the previous year than both INJ and FNG groups (p values < 0.001). Patients in NTZ group were also more disabled ($p = 0.007$) and were more likely to have GD-enhancement at baseline scan ($p = 0.003$) than those in INJ group. There were no differences between FNG and INJ groups, except for higher EDSS score in FNG group ($p = 0.038$).

Such between-group imbalance did not persist after the matching procedure that retained 330 patients (110 per group; Table 1). No covariate exhibited large imbalance ($|d| > 0.20$) in the re-sampled population (Fig. 2).

Primary outcome At follow-up, the proportion of patients with NEDA-3 was greater in NTZ group (67%) than both FNG (42%) and INJ (35%) groups (p values ≤0.034). The proportion of FNG-treated patients with NEDA-3 was greater than that of INJ group (42 vs. 35%, $p = 0.016$). The Fig. 3 shows the description of different components of NEDA 3 in the PS-matched population at the end of the 24-month follow-up.

Sensitivity analysis To alter the significant difference in the proportions with NEDA-3 between NTZ and INJ, the relative risk estimate and between-group prevalence imbalance of an hypothetical unmeasured binary confounder should be either >5.0 and 40%, or >9.0 and 20%, respectively.

To alter the significant difference in the proportions with NEDA-3 between FNG and INJ, as well as between NTZ and FNG, the relative risk estimate and between-group prevalence imbalance of an hypothetical unmeasured binary confounder should be either >2.0 and 40%, or >5.0 and 20%, respectively.

Secondary outcomes (Table 2) The risk of relapse was lower in NTZ group when compared with INJ group [hazard ratio (HR) = 0.37, $p < 0.001$] and FNG group (HR = 0.58, $p = 0.048$). The risk of relapse was also lower in FNG group when compared with INJ group (HR = 0.57, $p = 0.048$).

There were no differences across treatment groups in risk of disability worsening (p values ≥0.18).

The risk of radiological activity was lower in NTZ group when compared with both INJ group (HR = 0.28, $p < 0.001$) and FNG group (HR = 0.48, $p = 0.006$). The risk of radiological activity was also reduced in FNG group when compared with INJ group (HR = 0.51, $p = 0.006$).

Kaplan–Meier curves showing time to reach secondary outcomes are shown in Fig. 3.

Tertiary outcome (Fig. 4) Although the proportion of NTZ-treated (9%) and FNG-treated patients (7%) with disability reduction was higher than that of INJ-treated patients (1%), we found no significant difference across treatment groups ($p > 0.07$).

Dataset B

Participants We collected data from 216 highly active MS patients who started their first DMD following the diagnosis. Of them, 93 started high-dose, high-frequency IFNB (IFNB-1b 250 mcg every other day, $n = 42$; IFNB-1a 44 mcg thrice per week, $n = 51$), 63 started FNG, and 60 started NTZ (Fig. 1). Unadjusted comparisons of effectiveness among the three different DMDs showed no between-group difference in disability worsening, mainly due to the low proportion of patients reaching the outcome ($n = 30$, 13%). We also found that (1) NTZ was superior to

Fig. 1 Study flow chart and proportion of patients reaching outcomes before the propensity score matching procedure. Dataset A: non-responders to interferon beta or glatiramer acetate; dataset B: highly active treatment naives

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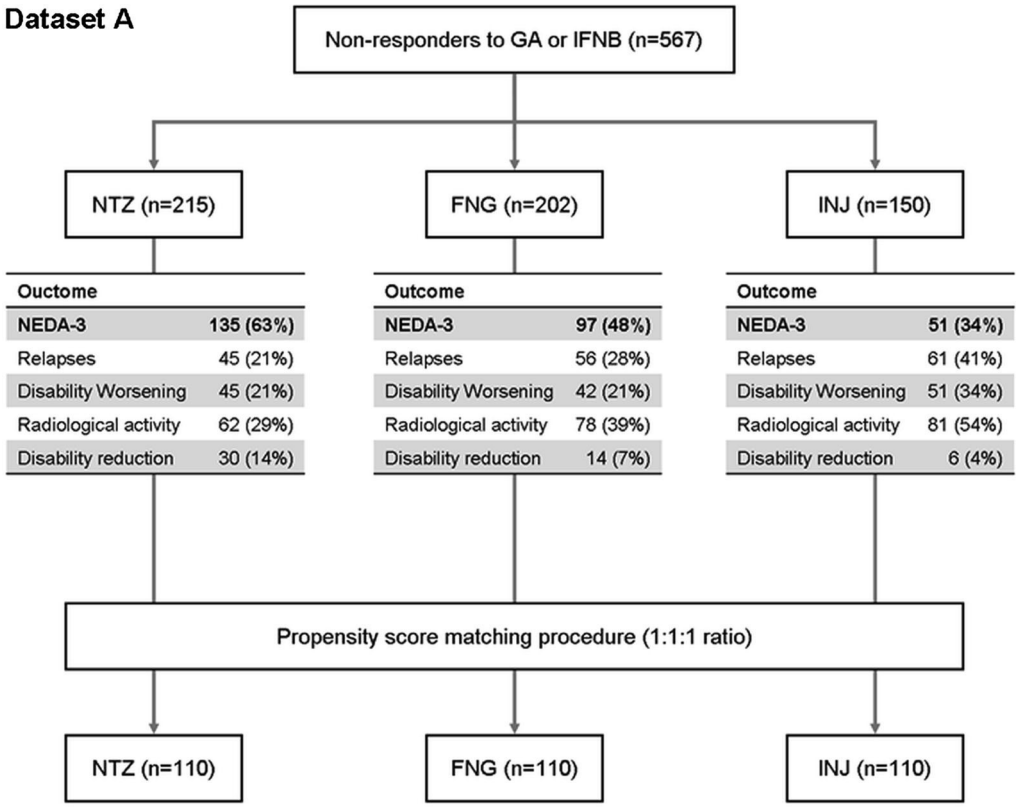

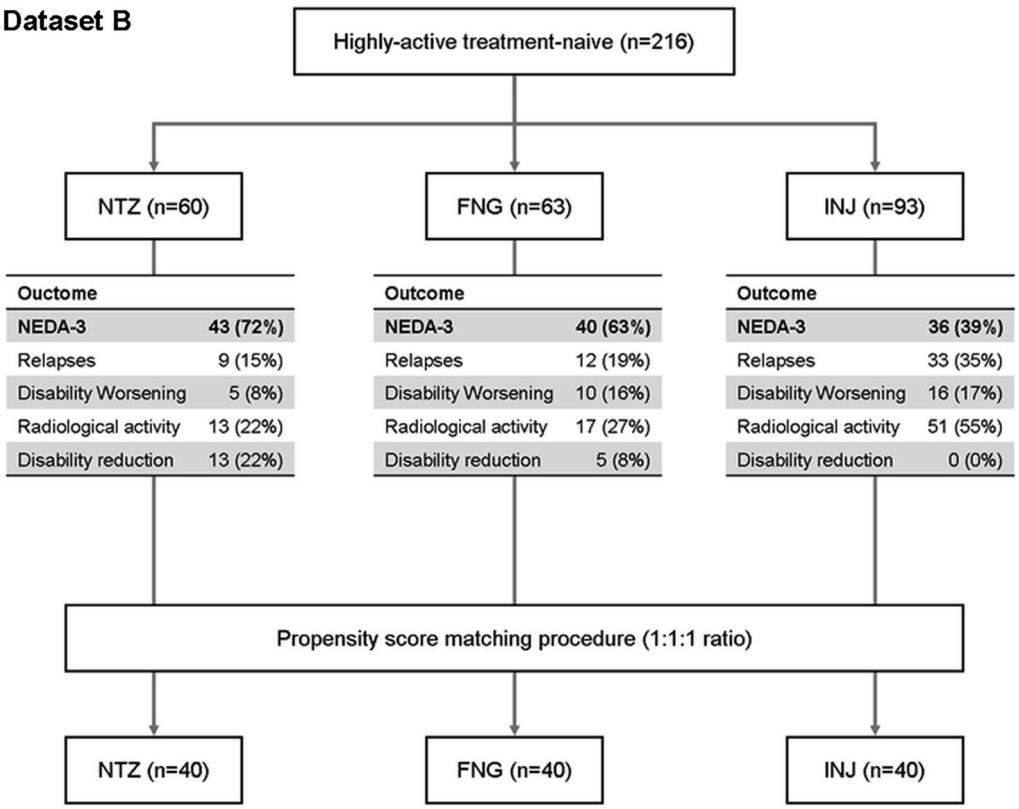

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Table 1 Dataset A: patients' characteristics at baseline (i.e. at DMA change after GA or IFNB failure)

	Whole sample			Propensity-score matched sample		
	INJ	FNG	NTZ	INJ	FNG	NTZ
N	150	202	215	110	110	110
Male sex, *n* (%)	49 (32.7)	54 (26.7)	64 (29.8)	33 (30.0)	35 (31.8)	27 (24.5)
Age, years	37.5 (8.7)	38.7 (9.7)	34.1 (9.3)	36.7 (8.8)	36.1 (9.2)	37.2 (9.4)
Time since first symptom, years	8.6 (6.4)	9.3 (7.2)	7.5 (5.3)	8.5 (6.3)	7.8 (5.8)	8.5 (5.8)
EDSS score	2.5 (1.2)	2.7 (1.3)	2.6 (1.2)	2.7 (1.3)	2.6 (1.1)	2.7 (1.1)
No. of relapse in previous year	1.3 (0.5)	1.4 (0.8)	1.7 (0.7)	1.4 (0.5)	1.4 (0.6)	1.4 (0.5)
Gadolinium-enhancement, *n* (%)	93 (62.0)	105 (52.0)	142 (66.0)	69 (62.7)	66 (60.0)	67 (60.9)

All values are mean (standard deviation), unless indicated otherwise

EDSS Expanded Disability Status Scale, *FNG* fingolimod, *INJ* self-injectable drugs, *NTZ* natalizumab

INJ in all remaining outcomes ($p < 0.01$); (2) FNG was superior to INJ in all remaining outcomes ($p < 0.05$); (3) there was no significant difference between NTZ and FNG in proportion of patients with NEDA-3, relapses, and radiological activity (p values >0.2), while NTZ was superior to FNG in promoting disability reduction ($p = 0.03$).

We observed significant imbalance in pre-matching baseline characteristics across treatment groups (Table 3). Post-hoc tests indicated that patients in INJ group had shorter time since first symptom and lower EDSS score than both FNG and NTZ groups (p values <0.05). Patients in INJ group were also younger ($p = 0.032$) and had fewer relapses in previous year than those ones in FNG group ($p = 0.002$).

There was no difference between NTZ and FNG groups, except for a greater number of relapses in previous year in NTZ group ($p = 0.038$). Such between-group imbalance did not persist after the matching procedure that retained 120 patients (40 per group; Table 3). No covariate exhibited large imbalance ($|d| > 0.20$) in the re-sampled population (Fig. 2).

Primary outcome At follow-up, the proportion of patients with NEDA-3 was greater in NTZ group (75%) and FNG group (67%) than INJ group (40%), but none of the comparisons reached the statistical significance (p values >0.06). Figure 3 shows the description of different components of NEDA 3 in the PS-matched population at the end of the 24-month follow-up.

Sensitivity analysis We did not perform the sensitivity analysis in dataset B because there was no difference in primary outcome across different treatment groups.

Secondary outcomes (Table 4) The risk of relapse was lower only in NTZ vs. INJ group (HR = 0.29, $p = 0.045$), while the comparison between FNG and INJ group was not significant (HR = 0.48, $p = 0.19$). The risk of relapse did not differ between NTZ and FNG ($p = 0.99$).

There was no difference across treatment groups in risk of both disability worsening (p values >0.08) and radiological activity (p values >0.09).

Kaplan–Meier curves showing time to reach secondary outcomes are shown in Fig. 3.

Tertiary outcome (Fig. 4) Disability reduction was more frequently observed in NTZ group (20%) than in both INJ group (20 vs. 0%, p = 0.009) and FNG group (5%); however, this latter figure did not reach the statistical significance ($p = 0.086$). There was no difference between FNG and INJ in probability of disability reduction ($p = 0.15$).

Discussion

Quasi-randomized post-marketing studies have compared so far one DMD with another in MS people [6–14]. However, neurologists can benefit from comparing the effectiveness of more than two appropriate treatment options. Therefore, here we sought to compare three treatment groups simultaneously by creating 1:1:1 PS-matched cohorts [24, 25, 29]. Moreover, we stratified the analyzes according to the past treatment history (non-responders to self-injectable DMD and highly active treatment-naïves) [16]. This allowed us to observe that, overall, highly active treatment-naïves experienced better outcomes compared with non-responders, regardless of treatment allocation. This latter finding reinforces the concept of a greater effectiveness of whichever DMD in patients with RR-MS who started treatment at younger age, with milder EDSS and a more active disease [15].

In line with literature data, unadjusted comparisons revealed that escalation to more active DMDs is better than lateral switch in patients who failed a GA or IFNB treatment [6–9], with NTZ superior to FNG in terms of NEDA-3, radiological activity, and disability reduction

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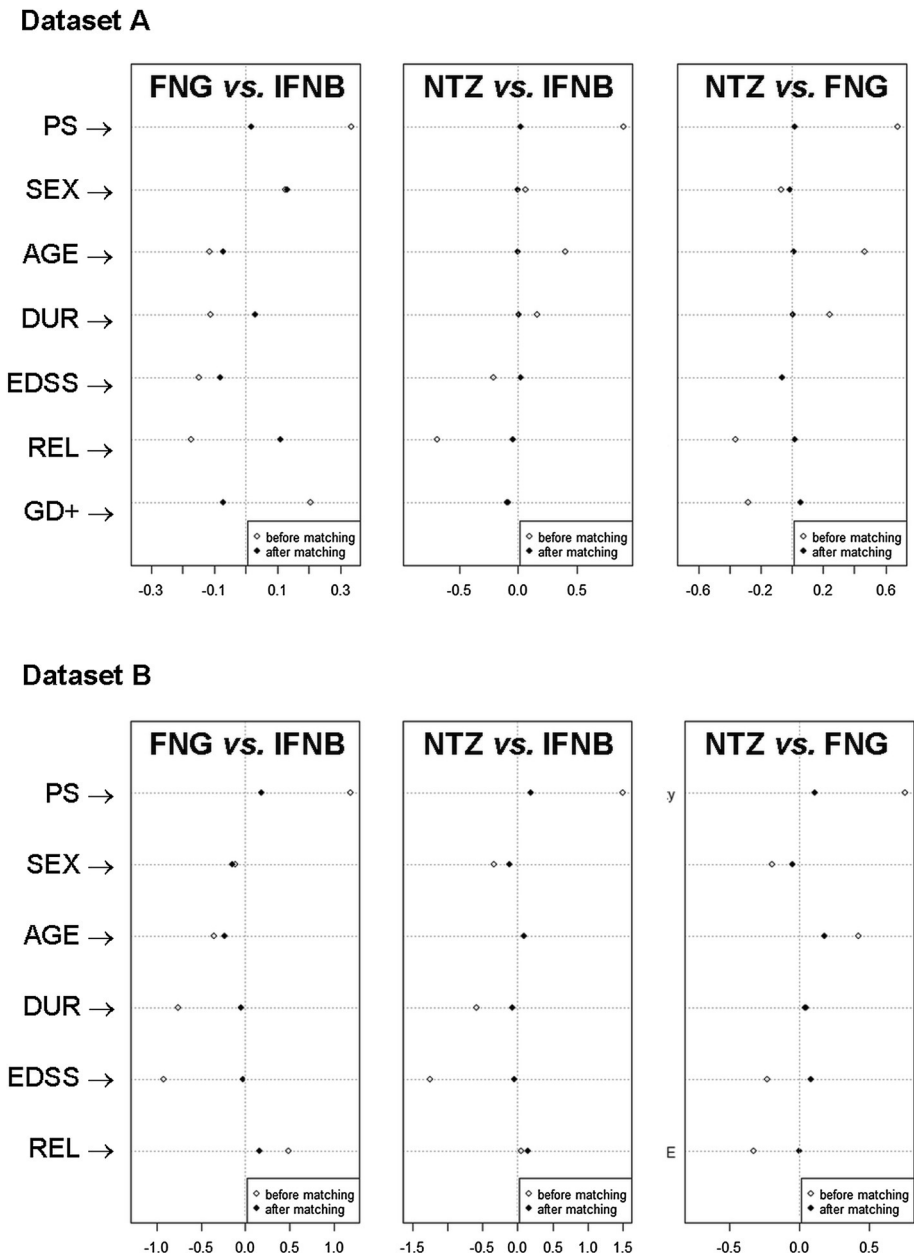

Fig. 2 Standardized differences (|d|) in baseline patients' characteristics for pairwise comparisons in dataset A and B before and after the propensity score matching procedure. *DUR* time since first symptom, *EDSS* Expanded Disability Status Scale, *GD+* presence of gadolinium-enhancement at baseline scan, *REL* number of relapses in the previous year

[11–13, 23, 30]. The PS-adjusted analysis confirms that, in our MS population, escalation to NTZ was the most effective choice after failure treatment with GA or IFNB, ensuring approximately a 2-fold (compared to INJ) and a 50% (compared to FNG) increased likelihood of NEDA-3 over a 24-month follow-up. The superiority of NTZ in the non-responder dataset was mainly driven by its effectiveness in reducing the risk of radiological activity and, to a lesser extent, in suppressing relapses over INJ and FNG. Notably, also FNG was superior over INJ in achieving NEDA-3 status, suppressing relapses and radiological activity. However, we found no difference across treatments in terms of disability worsening and disability reduction. We may speculate that the low proportion of patients reaching these two outcomes (about 25 and 6% for disability worsening and reduction, respectively) compromised the statistical power for detecting such between-group differences [31, 32].

In highly active treatment-naïves, unadjusted comparisons revealed that both NTZ and FNG were more effective than INJ in achieving the NEDA-3 status over the 24-month follow-up. The superiority of "second-generation" DMD (NTZ and FNG) over the "first-generation" DMD (high-dose, high-frequency IFNB) was mainly driven by a greater effectiveness on reducing the risk of relapse and radiological activity, while the overall small proportion of patients

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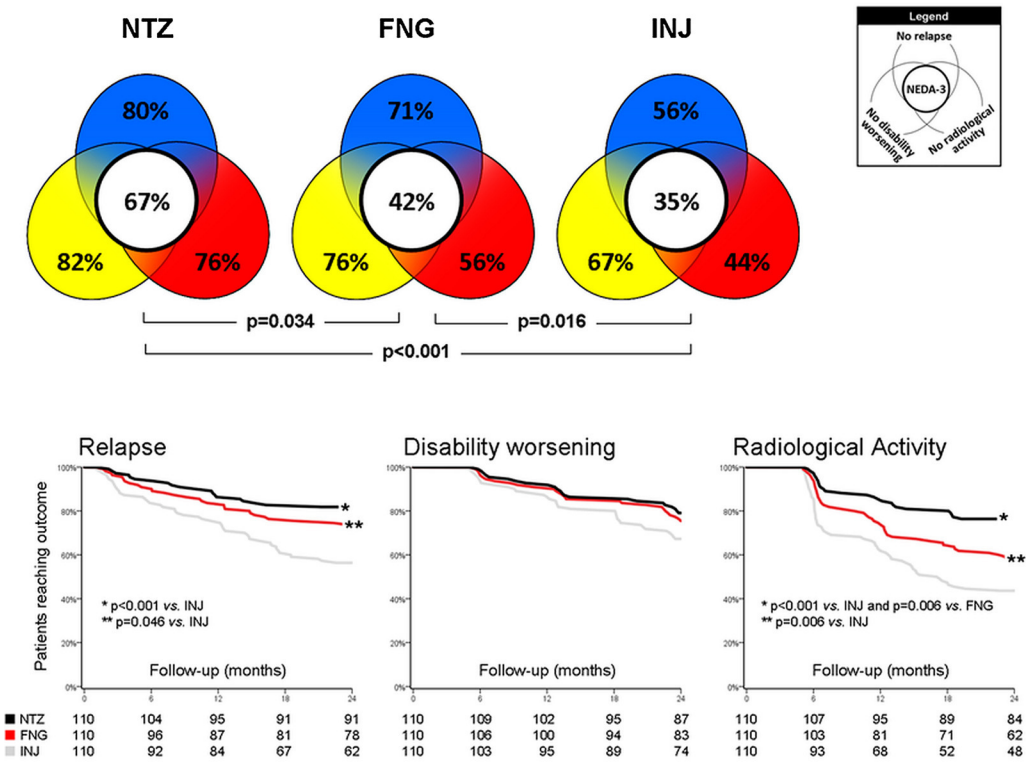
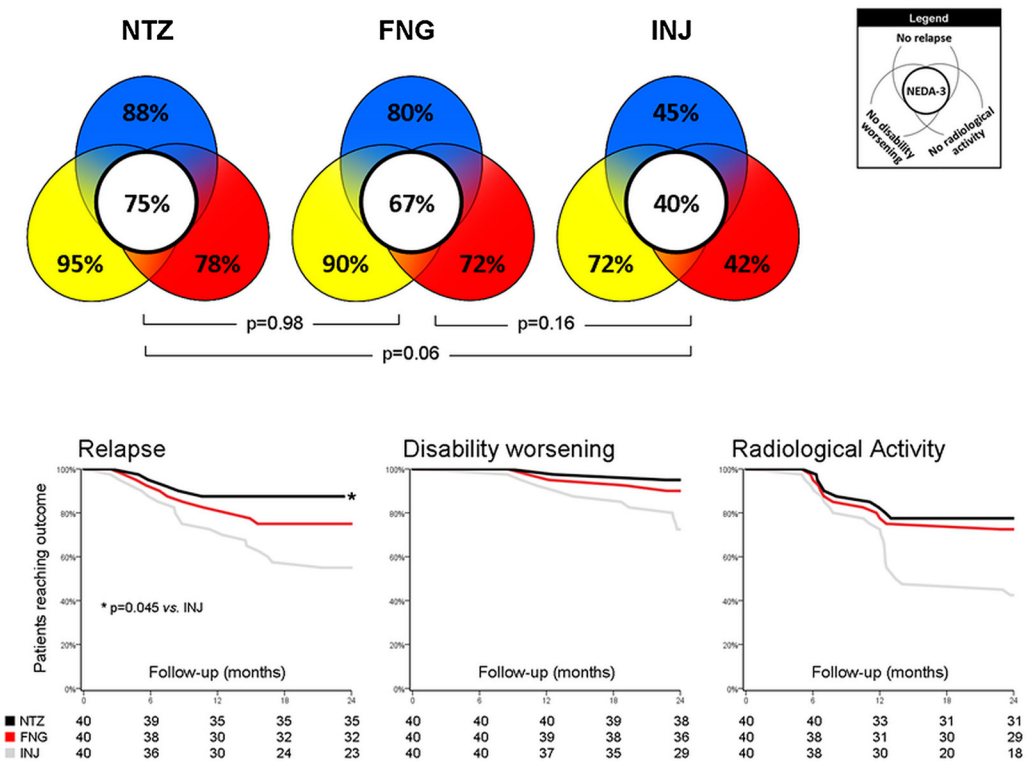
Dataset A



Dataset B



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◀**Fig. 3** Primary and secondary outcomes (no evidence of disease activity and its components) investigated in propensity score-matched subsamples (dataset A: 110 patients per group; dataset B: 40 patients per group). *p* values are corrected using the Bonferroni–Holm method. *FNG* fingolimod, *INJ* self-injectable drugs, *NEDA-3* no evidence of disease activity, *NTZ* natalizumab

experiencing disability worsening (about 15%) prevented the detection of any between-group difference. We did not find any difference between NTZ and FNG groups in all (NEDA-3, relapses, radiological activity) but one outcome (disability reduction), thus confirming that NTZ can promote functional recovery in MS people [11, 13, 23, 30].

Table 2 Cox regression models (adjusted by propensity score inverse weighting) to reach secondary outcomes in non-responders [re-sampled dataset A, $n = 330$; patients per group, $n = 110$], i.e. patients who experienced ≥2 relapses or 1 relapse associated with residual disability in the last year while on glatiramer acetate or interferon beta

	n (%) reaching the outcome	HR	95% CIs	*p**
Relapses				
NTZ vs. INJ	22 (20%) vs. 48 (44%)	0.37	0.22–0.65	**<0.001**
FNG vs. INJ	32 (29%) vs. 48 (44%)	0.57	0.35–0.93	**0.046**
NTZ vs. FNG	22 (20%) vs. 32 (29%)	0.58	0.31–1.08	0.087
Disability worsening				
NTZ vs. INJ	20 (18%) vs. 36 (33%)	0.58	0.33–1.02	0.18
FNG vs. INJ	27 (24%) vs. 36 (33%)	0.63	0.37–1.07	0.18
NTZ vs. FNG	20 (18%) vs. 27 (24%)	0.94	0.51–1.74	0.84
Radiological activity				
NTZ vs. INJ	26 (24%) vs. 62 (56%)	0.28	0.17–0.46	**<0.001**
FNG vs. INJ	48 (44%) vs. 62 (56%)	0.51	0.33–0.80	**0.006**
NTZ vs. FNG	26 (24%) vs. 48 (44%)	0.48	0.28–0.81	**0.006**

FNG fingolimod, *INJ* self-injectable drugs, *NTZ* natalizumab

* By the Bonferroni–Holm correction for multiple comparisons

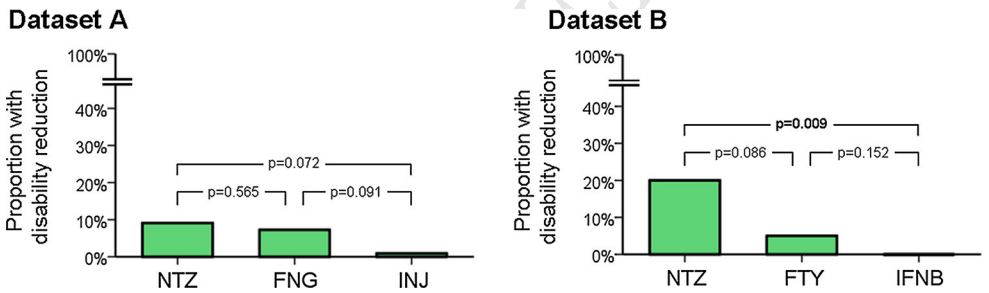

Fig. 4 Tertiary outcome (disability reduction) in propensity score-matched subsamples (dataset A: 110 patients per group; dataset B: 40 patients per group). *p* values are corrected using the Bonferroni–Holm method. *FNG* fingolimod, *INJ* self-injectable drugs, *NEDA-3* no evidence of disease activity, *NTZ* natalizumab

Table 3 Dataset B: patients' characteristics at baseline (i.e. at treatment start)

	Whole sample			Propensity-score matched sample		
	IFN	FNG	NTZ	IFN	FNG	NTZ
N	93	63	60	40	40	40
Male sex, *n* (%)	29 (31.2%)	23 (36.5%)	28 (46.7%)	13 (32.5%)	15 (37.5%)	16 (35%)
Age, years	30.3 (8.7)	33.4 (8.9)	29.4 (11.4)	32.2 (8.9)	32.1 (9.3)	30.4 (7.8)
Time since first symptom, years	1.8 (2.3)	3.6 (4.3)	3.2 (3.7)	2.1 (1.7)	2.3 (2.9)	2.2 (2.2)
EDSS score	1.8 (0.8)	2.5 (1.1)	2.8 (1.4)	2.1 (0.9)	2.1 (0.9)	2.1 (0.8)
No. of relapse in previous year	2.2 (0.6)	2.0 (0.7)	2.1 (0.8)	2.1 (0.5)	2.1 (0.6)	2.1 (0.7)

All values are mean (standard deviation), unless indicated otherwise

EDSS Expanded Disability Status Scale, *FNG* fingolimod, *INJ* self-injectable drugs, *NTZ* natalizumab

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Table 4 Cox regression models (adjusted by propensity score inverse weighting) to reach secondary outcomes in highly active treatment-naives [re-sampled dataset B, $n = 120$; patients per group, $n = 40$], i.e. patients who were never treated before with any disease-modifying drugs and experienced ≥1 relapse in the last year and 1≥ gadolinium-enhancement at brain or spinal cord scan

	n (%) reaching the outcome	HR	95% CIs	*p**
Relapses				
NTZ vs. INJ	5 (12%) vs. 17 (42%)	0.29	0.11–0.81	**0.045**
FNG vs. INJ	8 (20%) vs. 17 (42%)	0.48	0.20–1.12	0.19
NTZ vs. FNG	5 (12%) vs. 8 (20%)	0.99	0.25–3.99	0.99
Disability worsening				
NTZ vs. INJ	2 (5%) vs. 11 (27%)	0.18	0.04–0.82	0.081
FNG vs. INJ	4 (10%) vs. 11 (27%)	0.39	0.12–1.25	0.22
NTZ vs. FNG	2 (5%) vs. 4 (10%)	0.40	0.08–5.32	0.37
Radiological activity				
NTZ vs. INJ	9 (22%) vs. 22 (55%)	0.42	0.19–0.93	0.096
FNG vs. INJ	11 (27%) vs. 22 (55%)	0.50	0.24–1.05	0.13
NTZ vs. FNG	9 (22%) vs. 11 (27%)	0.99	0.38–2.57	0.99

FNG fingolimod, *INJ* self-injectable drugs, *NTZ* natalizumab

* By the Bonferroni–Holm correction for multiple comparisons

Unfortunately, the PS-based re-sampling of dataset B resulted in small cohort sizes and, therefore, we cannot completely rule out that the borderline *p* values observed for most comparisons are due to the low statistical power. However, we are aware that the use of NTZ or FNG as first treatment option is restricted by enrolment criteria in Italy [15], making difficult to reach large sample sizes even in a multicentre observational study.

The performance of FNG, better in highly active treatment-naives than in non-responder ones, is only partially surprising. Although the European Medicines Agency (EMA) denied registration of FNG as first-line therapy, in United States the Food and Drug Administration (FDA) allowed prescription of FNG as first-line DMD in relapsing MS. Furthermore, the successful FREEDOMS and TRANSFORMS trials mainly enrolled patients without any previous treatment history (more than 50%), thus supporting its use as first treatment rather than second-line option [33, 34].

In conclusion, we provide real-world data comparing effectiveness of widely used DMDs in non-responders to IFNB or GA and in highly active treatment naives. Percentages of patients with NEDA-3 widely varied even within the same DMD according to previous treatment history, especially in FNG-treated patients. However, our study is only hypothesis-generating and suffers from several limitations, as the small sample size of some treatment groups (as discussed above), comparison of patients in different treatment era, lack of randomization, and hidden biases that were only partially dealt with sensitivity analyzes.

On the other hand, we adopted robust statistical models to enhance the validity of our findings and to provide a minimally biased picture of the real-world clinical experience in the newer treatment era.

Compliance with ethical standards

Conflicts of interest No conflict of interest.

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Schering, Biogen, Genzyme, Merck Serono, Novartis, Roche and Teva.

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