Natalizumab Versus Fingolimod in Patients with Relapsing-Remitting Multiple Sclerosis: A Subgroup Analysis From Three International Cohorts

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Abstract

Introduction Natalizumab has proved to be more effective than fingolimod in reducing disease activity in relapsing-remitting multiple sclerosis (RRMS). Whether this association is universal for all patient groups remains to be determined.

Objective The aim of this study was to compare the relative effectiveness of natalizumab and fingolimod in RRMS subgroups defined by the baseline demographic and clinical characteristics of interest.

Methods Patients with RRMS who were given natalizumab or fingolimod were identified in a merged cohort from three international registries. Efficacy outcomes were compared across subgroups based on patients' sex, age, disease duration, Expanded Disability Status Scale (EDSS) score, and disease and magnetic resonance imaging (MRI) activity 12 months prior to treatment initiation. Study endpoints were number of relapses (analyzed with weighted negative binomial generalized linear model) and 6-month confirmed disability worsening and improvement events (weighted Cox proportional hazards model), recorded during study therapy. Each patient was weighted using inverse probability of treatment weighting based on propensity score.

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Results A total of 5148 patients (natalizumab 1989; fingolimod 3159) were included, with a mean $\pm$ standard deviation age at baseline of 38 $\pm$ 10 years, and the majority (72%) were women. The median on-treatment follow-up was 25 (quartiles 15–41) months. Natalizumab was associated with fewer relapses than fingolimod (incidence rate ratio [IRR]; 95% confidence interval [CI]) in women (0.76; 0.65–0.88); in those aged $\leq$ 38 years (0.64; 0.54–0.76); in those with disease duration $\leq$ 7 years (0.63; 0.53–0.76); in those with EDSS score < 4 (0.75; 0.64–0.88), < 6 (0.80; 0.70–0.91), and $\geq$ 6 (0.52; 0.31–0.86); and in patients with pre-baseline relapses (0.74; 0.64–0.86). A higher probability of confirmed disability improvement on natalizumab versus fingolimod (hazard ratio [HR]; 95% CI) was observed among women (1.36; 1.10–1.66); those aged > 38 years (1.34; 1.04–1.73); those with disease duration > 7 years (1.33; 1.01–1.74); those with EDSS score < 6 (1.21; 1.01–1.46) and $\geq$ 6 (1.93; 1.11–3.34); and patients with no new MRI lesion (1.73; 1.19–2.51).

Conclusions Overall, in women, younger patients, those with shorter disease durations, and patients with pre-treatment relapses, natalizumab was associated with a lower frequency of multiple sclerosis relapses than fingolimod. It was also associated with an increased chance of recovery from disability among most patients, particularly women and those with no recent MRI activity.

Key Points

Natalizumab was superior to fingolimod in reducing relapse activity, mainly among women, younger patients, those with shorter disease duration, and patients with pre-treatment relapses.

Disability improvement was more commonly associated with natalizumab than with fingolimod, particularly among women and patients without brain or spinal cord magnetic resonance imaging activity preceding treatment start.

The effectiveness of natalizumab and fingolimod on disability worsening was comparable across the studied subgroups.

1 Introduction

Natalizumab and fingolimod, two high-efficacy disease-modifying therapies for multiple sclerosis (MS), both reduce relapse rates, localized inflammatory activity detected on magnetic resonance imaging (MRI), and risk of disability worsening [1, 2]. Evidence from some but not all observational comparative analyses suggests a superior effect of natalizumab, especially in patients with active disease [3–6]. However, the activity and the severity of MS varies considerably among patients, and studies have shown that patients of different demographic and clinical characteristics respond to treatment differently [7]. In a subgroup analysis of the AFFIRM and SENTINEL trials, natalizumab was found to be more effective than placebo/interferon-β1a in reducing the risk of sustained disability worsening in the following subgroups: women, patients aged < 40 years, patients with nine or more T_2 lesions, and patients with at least one gadolinium-enhancing (Gd+) lesion at baseline [8]. In a subgroup analysis

of the phase III FREEDOMS study, compared with placebo, fingolimod was most effective at reducing the risk of disability worsening in males, patients who were naïve to previous treatment, patients with baseline Expanded Disability Status Scale (EDSS) score > 3.5, and those with T_2 lesion volume > 3300 mm^3 [9]. However, a head-to-head comparison of the effectiveness of natalizumab versus fingolimod in different subgroups of patients is yet to be explored.

The objective of this study was to determine the relative effectiveness of natalizumab and fingolimod across subgroups of patients with relapsing-remitting MS (RRMS), using data from three large international registries, stratified by clinical and demographic characteristics. This study is the second in a series of three studies. The first study, based on three published studies [3, 4, 10] of head-to-head comparisons of natalizumab and fingolimod from the three cohorts, evaluated the differences in effectiveness between the two therapies in the combined cohort and quantified heterogeneity in the data from the three registries. Two of the three original studies [3, 4] showed that natalizumab was more effective than fingolimod in the prevention of relapses and disability worsening, whereas the third study [10] reported no difference. The pooled analysis confirmed the superior effect of natalizumab over fingolimod in disability improvement and reduced relapse incidence in patients who had experienced breakthrough disease activity on first-line therapy [11]. This second study set out to identify subgroups of patients who would benefit most from the superior effectiveness of natalizumab versus fingolimod.

2 Methods

2.1 Ethics Statement

MSBase is an international MS registry (World Health Organization International Clinical Trials Registry ID: ACTRN12605000455662) of observational data collected longitudinally as part of routine clinical care from 129

mostly tertiary MS centres in 36 countries [12]. MSBase was approved by the Melbourne Health Human Research Ethics Committee and by the site institutional review boards, unless exemptions were granted according to local regulations. Written informed consent was obtained from enrolled patients.

OFSEP (Observatoire Français de la Sclérose en Plaques; French MS registry), ClinicalTrials.gov ID: NCT02889965, prospectively collects longitudinal data on clinical, biological, and imaging markers from patients who provided written informed consent following the French law on Bioethics [13]. The storage of data for research purposes was approved by the French Commission Nationale de l'Informatique et des Libertés.

The Danish Multiple Sclerosis Registry (DMSR) is a nationwide population-based registry consisting of longitudinal data from all patients receiving disease-modifying therapies [14]. Data are collected prospectively and stored according to the data protection law of the Danish Data Inspection. The Center for Data Review applications approved the study (j. nr. 2012-58-0004/VD-2018-121 I-suite 6361).

2.2 Study Population, Intervention, and Follow-Up

Longitudinal demographic and clinical data were extracted from MSBase on 15 May 2018. The MSBase data are entered in the iMed or MSBase online data entry system and are subject to minimum annual updates. Data quality was assessed prior to data extraction as per standard MSBase procedures [15].

The OFSEP cohort included data from 27 French university hospitals extracted from European Database for Multiple Sclerosis (EDMUS) software [16] in July 2014. An automated consistency check was performed using the EDMUS software.

The DMSR cohort was extracted from the Danish MS Registry on 1 March 2018.

Only patients with RRMS who started natalizumab or fingolimod (study therapy) for the first time on or after 1 January 2011 and continued for a minimum of 3 months were included in this study. For each patient, baseline was the recorded date of commencement of a study therapy. Each patient was only allowed to contribute one instance of exposure to a study therapy. Where multiple starts of a study therapy were recorded, the earliest eligible treatment exposure was used. Patients were censored at discontinuation or change of study therapy or end of follow-up, whichever occurred first. The minimum dataset included date of birth, sex, date of first clinical presentation, date of relapses, disease course, EDSS score recorded within 6 months before and 1 month after treatment initiation, and two post-baseline visits 6 months apart with EDSS score

recorded, with at least one while on treatment. Patients who underwent hematopoietic stem cell therapy, participated in randomized trials involving studied agents, or were treated with cyclophosphamide, cladribine, mitoxantrone, daclizumab, rituximab, ocrelizumab, or alemtuzumab before baseline were excluded. The reported MRI information during the year preceding study baseline was also used for analysis stratified by MRI activity (this was available only from the MSBase and OFSEP databases). The OFSEP imaging protocol mandates at least one brain MRI every 3 years and one spinal cord MRI every 6 years performed at most 1 month before the consultation with the neurologist. MSBase protocol stipulates that brain MRI is performed annually. In total, 78.8% of the patients from the OFSEP cohort had pre-baseline data on Gd+ T_1 lesions and new hyperintense T_2 lesions. In the MSBase cohort, 42.5% of the patients had data on Gd+ T_1 lesions (representing inflammatory breakdown of the blood–brain barrier preceding the pre-baseline MRI by up to 6 weeks), and 26.2% had data on new hyperintense T_2 lesions (which refer to interval MRI activity since the preceding brain MRI). To deal with the missing data, we conducted a complete-case subgroup analysis in a subset of patients with available pre-baseline MRI data (see Sect. 2.4).

2.3 Study Outcomes

Three clinical outcomes were evaluated to compare the relative effectiveness of the two study therapies in each patient subgroup:

(i) Time to first relapse and number of on-treatment relapses.

(ii) Time to first and multiple 6-month confirmed disability worsening events. Worsening of disability was defined by an increase of ≥ 1.5 or 1.0 or 0.5 EDSS steps if baseline EDSS score was 0 or 1.0–5.5 or > 5.5, respectively, that was sustained at all consecutive visits over ≥ 6 months, with confirmation not preceded by a relapse within 30 days [17].

(iii) Time to first and multiple 6-month confirmed disability improvement events. An improvement was defined as a decrease of 1.5 or ≥ 1.0 or 0.5 EDSS steps if baseline EDSS score was 1.5 or 2.0–6.0 or > 6.0, respectively, sustained at all consecutive visits over ≥ 6 months.

The EDSS score was re-baselined after each confirmed disability worsening or improvement event to adjust for fluctuation in EDSS scores [18]. Minimum EDSS score of the visits recorded during the 6-month confirmation period was used as a new baseline for evaluation of the next disability worsening or improvement event [17].

2.4 Statistical Analyses by Subgroups

Patients meeting the inclusion criteria were divided into subgroups based on sex, age at baseline (by median), disease duration from symptom onset to start of treatment (by median), baseline EDSS score (< 4.0, 4.0–5.5, < 6.0, ≥ 6.0), disease activity (relapse with or without disability worsening/disability worsening without relapse/none), and MRI activity (not observed/observed any new hyperintense T_2 or Gd+ T_1 lesions) in the year prior to baseline.

All patient records were weighted using inverse probability of treatment weighting (IPTW) based on the propensity score [3, 19]. The subgroup-specific propensity score was generated using multivariable generalized linear mixed models with treatment allocation (natalizumab/fingolimod) as the outcome variable and demographic and clinical variables available at study baseline as the independent variables. The independent variables included sex, age, EDSS score, and disease duration at baseline, number of relapses, evidence of disease activity (relapse, worsening of disability, or both) in the year preceding baseline, and number of previous disease-modifying therapies. Subgroup-specific variables, for example, sex, were not included in the multivariable models used to generate the propensity score for the subgroups of men and women. Country was modeled as a random effect. Weight for each patient was then computed, which was the ratio between the mean probability of receiving the treatment and the predicted probability of receiving that treatment for the given patient, obtained from the multivariable generalized linear mixed model.

Cumulative hazard of a first relapse (i.e., probability of remaining relapse free) was analyzed using a weighted Cox proportional hazards model with robust variance estimation. Counts of on-treatment relapses were modelled using a weighted negative binomial generalized linear model with logarithm of the study follow-up time as an offset. Cumulative hazard of a first disability worsening and improvement were evaluated separately using a weighted Cox proportional hazards model with robust variance estimation, adjusted for annualized visit density (visits per year). We used the weighted Andersen–Gill model to analyze multiple worsening and improvement events observed in a patient. Proportional hazards assumption was assessed with Schoenfeld residuals, and violation of the assumption was corrected by introducing an interaction term of the relevant variable with a time variable. All analyses were performed using R (version 3.4.0) [20].

3 Results

A total of 5148 patients fulfilling the inclusion criteria were identified in the three registry datasets (Fig. 1). The mean age of the patients at baseline was 38 ± standard deviation (SD) 10 (range 12–77) years with a median disease duration of 6.9 (quartiles 3.1–12.5) years. The majority (72%) of the patients were women. Pre-baseline MRI data were available for 47.5 and 78.8% patients in the MSBase and OFSEP cohorts, respectively. Table 1 shows patient baseline characteristics. Overall, 1989 patients received natalizumab and 3159 received fingolimod, with median (quartiles) on-treatment follow-up times of 24 (15–38) and 26 (15–43) months, respectively (Table 2). Annualized visit density with EDSS score recorded as expected was higher for patients treated with natalizumab than for those receiving fingolimod (Table 2). Standardized mean differences were calculated to compare the balance in baseline characteristics between the two treatment groups (Table 3). Five of the seven covariates used in the generalized linear mixed model to estimate the propensity score had a standardized mean difference that exceeded 10%, indicating imbalance in these covariates between treatment groups. The largest differences were observed for number of relapses in the year preceding baseline (36.8%) and EDSS score at baseline (32.0%). Weighting by the inverse probability of treatment substantially improved the balance between groups (Table 3). The largest standardized difference in the weighted sample was 4.5% (for EDSS score at baseline). Table 4 shows the baseline characteristics of the patients in the weighted sample.

3.1 Sex

The mean ± SD age of female patients at baseline was 38 ± 10 years with median (quartiles) disease duration of 7.2 (3.3–12.9) years and median (quartiles) EDSS score of 2.5 (1.5–3.5). Male patients included in the analyses were slightly younger, with a mean ± SD age of 37 ± 10 years. The median EDSS score of the male patients was the same as that of the female patients, with a slightly shorter median (quartiles) disease duration of 6.2 (2.8–11.8) years.

Among the women, the incidence rate ratio (IRR) of on-treatment relapse was lower with natalizumab than with fingolimod (IRR 0.76; 95% confidence interval [CI] 0.65–0.88; Fig. 2), which was supported by a lower likelihood of first relapse among natalizumab-treated patients (hazard ratio [HR] 0.79; 95% CI 0.63–0.98).

Natalizumab was also associated with a higher chance of disability improvement among women. The probability of the first confirmed disability improvement was 1.40 (95% CI 1.13–1.73; Fig. 3) times higher in women treated with natalizumab than in those on fingolimod. The cumulative probability of multiple disability improvement events confirmed the benefit of natalizumab over fingolimod (HR 1.36; 95% CI 1.10–1.66).

We did not find any evidence for difference in the risk of any of the studied outcomes among men (Figs. 2, 3 and 4).

Fig. 1 Flow diagram of patients included in the analyses. *DMT* disease-modifying therapy, *FTY* fingolimod, *MS* multiple sclerosis, *NAT* natalizumab, *RCT* randomized controlled trial, *RR* relapsing-remitting
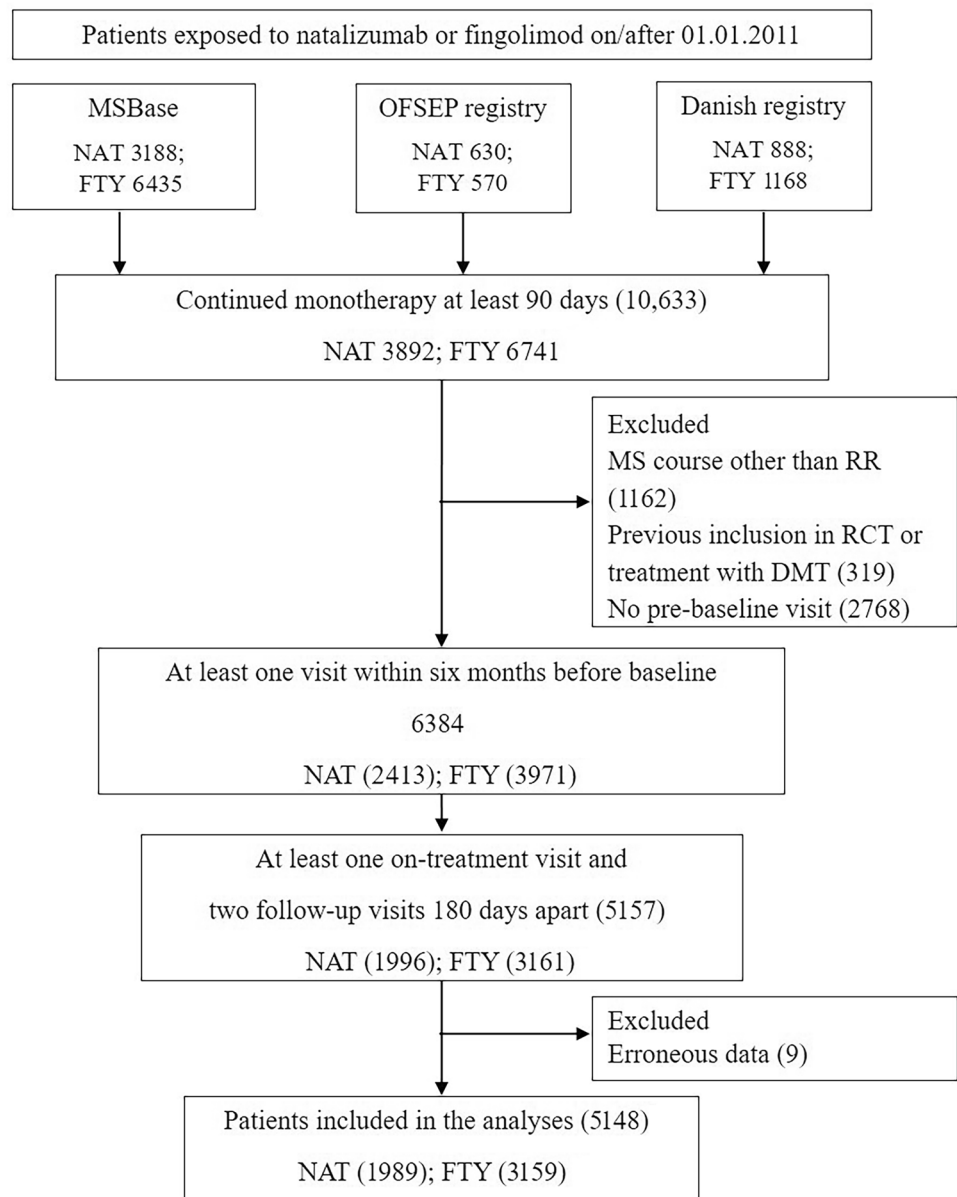
3.2 Age at Baseline

Older age at baseline was associated with longer disease duration and higher EDSS score (Table 1).

Natalizumab was associated with a lower incidence of on-treatment relapses than fingolimod in patients aged ≤38 years (IRR 0.64; 95% CI 0.54–0.76; Fig. 2). The probability of first relapse was also lower (HR 0.66; 95% CI 0.55–0.78) among patients of this age group who were treated with natalizumab.

However, patients aged >38 years experienced a 1.34 times (Fig. 3) higher chance of disability improvement as estimated for the first (HR 1.34; 95% CI 1.03–1.75) and multiple (HR 1.34; 95% CI 1.04–1.73) improvement events when treated with natalizumab compared with fingolimod.

Similar trends, but of a marginally smaller magnitude, were also seen among patients aged ≤38 years.

3.3 Disease Duration at Baseline

Patients with disease duration ≤ 7 years were on average younger and had lower median EDSS scores than patients with disease duration > 7 years (Table 1).

Among the subgroup with shorter disease duration (≤ 7 years), natalizumab was associated with a lower risk of first relapse (HR 0.66; 95% CI 0.56–0.79; Fig. 2) and a lower relapse rate than was fingolimod (IRR 0.63; 95% CI 0.53–0.76).

The chance of disability improvement trended towards higher with natalizumab in both subgroups (disease duration

Table 1 Baseline characteristics of study subgroups

Characteristics	Sample size	Sex (% women)	Age, years	Disease duration, years	EDSS score
Sex					
Men	1450	–	37 ± 10	6.2 (2.8–11.8)	2.5 (1.5–3.5)
Women	3698	–	38 ± 10	7.2 (3.3–12.9)	2.5 (1.5–3.5)
Age, years					
≤ 38	2616	70	–	5.0 (2.2–8.8)	2.0 (1.5–3.0)
> 38	2532	74	–	10.0 (4.9–16.2)	3.0 (2.0–4.0)
Disease duration, years					
≤ 7	2587	70	33 (27–41)	–	2.0 (1.5–3.0)
> 7	2561	74	41 ± 9	–	3.0 (2.0–4.0)
EDSS score					
< 4	3940	72	36 (30–43)	6.1 (2.7–11.0)	–
4–5.5	932	72	41 ± 10	10.1 (5.6–16.4)	–
< 6	4872	72	37 (30–44)	6.7 (3.0–12.2)	–
≥ 6	276	75	44 ± 11	11.0 (6.2–17.9)	–
Disease activity within 12 months before BL					
Relapse with or without disability worsening	3291	71	37 ± 10	6.5 (2.7–12.1)	2.5 (1.5–3.5)
Disability worsening without relapse	419	70	39 ± 10	8.1 (4.3–13.9)	3.0 (2.0–4.0)
None	1438	74	40 (33–46)	7.6 (3.8–13.2)	2.0 (1.5–3.5)
MRI activity reported within 12 months before BL	French MS registry: 324 (T_1: 324; T_2: 324) MSBase registry: 1563 (T_1: 1400; T_2: 864)				
No evidence of new or active lesion	623	71	39 (32–46)	7.9 (4.1–13.1)	2.5 (1.5–4.0)
≥ 1 new hyperintense T_2 lesion or Gd+ T_1 lesion	1264	73	34 (27–42)	5.6 (2.3–10.1)	2.0 (1.5–3.0)

Data are presented as mean $\pm$ standard deviation or median (quartiles) unless otherwise indicated

BL baseline, *EDSS* Expanded Disability Status Scale, *Gd+* gadolinium enhancing, *MRI* magnetic resonance imaging, *MS* multiple sclerosis

Table 2 Treatment duration and number of visits with Expanded Disability Status Scale scores recorded per year by treatment in the three registries

Registry	Treatment duration, months		EDSS scores recorded per year	
	Natalizumab	Fingolimod	Natalizumab	Fingolimod
Combined cohort	24 (15–38)	26 (15–43)	2.5 (1.8–4.3)	2.2 (1.6–3.2)
Danish MS registry	31 (19–49)	41 (24–56)	2.3 (1.8–3.0)	2.0 (1.6–2.3)
French MS registry	24 (18–30)	18 (14–23)	3.0 (1.8–11.8)	2.3 (1.8–3.0)
MSBase registry	22 (13–34)	24 (13–38)	2.7 (1.8–4.9)	2.5 (1.6–3.9)

Data are presented as median (quartiles)

EDSS Expanded Disability Status Scale, *MS* multiple sclerosis

≤ 7 years [HR 1.17; 95% CI 0.93–1.47] and > 7 years [HR 1.33; 95% CI 1.01–1.74]; Fig. 3).

3.4 Baseline Expanded Disability Status Scale Score

Patients from the subgroups with higher baseline EDSS scores tended to be older and have longer disease durations than those with lower EDSS scores (Table 1).

In the subgroup of those with EDSS scores < 4, natalizumab was more efficient than fingolimod at reducing on-treatment number of relapses (IRR 0.75; 95% CI 0.64–0.88; Fig. 2). Among patients with EDSS scores 4–5.5, no substantial difference in the effectiveness of natalizumab and fingolimod on reducing relapse frequency was seen. However, patients with EDSS scores < 6 who were treated with natalizumab experienced fewer relapses (IRR 0.80; 95% CI

Table 3 Standardized mean differences in unweighted and weighted samples

Characteristics	Unweighted			Weighted		
	Natalizumab	Fingolimod	SMD (%)	Natalizumab	Fingolimod	SMD (%)
Sex						
Men	27.05%	28.87%	4.06	28.46%	28%	1.02
Women	72.95%	71.13%	4.06	71.54%	72%	1.02
Age at BL, years	36.95 ± 10.35	38.52 ± 9.84	15.54	38.2 ± 10.59	37.97 ± 9.88	2.23
Disease duration at BL, years	7.99 ± 6.97	9.1 ± 7.18	15.72	8.81 ± 7.65	8.67 ± 6.97	2.03
BL EDSS score	2.95 ± 1.58	2.45 ± 1.53	32.01	2.73 ± 1.52	2.66 ± 1.59	4.53
Number of relapses 12 months before BL	1.18 ± 1.03	0.83 ± 0.85	36.76	0.99 ± 0.94	0.97 ± 0.97	2.05
Number of previous DMT	1.27 ± 1	1.36 ± 0.94	8.38	1.33 ± 1.05	1.33 ± 0.93	0.02
Disease activity 12 months before BL						
Disability worsening without relapse	160 (8.04)	259 (8.2)	0.57	8.42%	8.41%	0.03
Relapse without disability worsening	886 (44.54)	1273 (40.3)	8.6	42.15%	41.48%	1.34
Relapse with disability worsening	533 (26.8)	599 (18.96)	18.74	22.9%	22.1%	1.92
None	410 (20.61)	1028 (32.54)	27.25	26.54%	28.01%	3.31

Data are presented as *n* (%) or mean ± standard deviation unless otherwise indicated

BL baseline, *DMT* disease-modifying therapy, *EDSS* Expanded Disability Status Scale, *SMD* standardized mean difference

0.70–0.91) than did patients treated with fingolimod. The largest relative reduction in relapse incidence associated with natalizumab was observed among patients with EDSS scores ≥ 6 (IRR 0.52; 95% CI 0.31–0.86).

Among patients with EDSS scores 4–5.5, the disability improvement tended to be more frequent with natalizumab than with fingolimod (HR 1.37; 95% CI 0.98–1.90; Fig. 3). However, natalizumab was estimated to accelerate recovery by 1.21 times in patients with EDSS scores <6, confirmed by first (95% CI 1.01–1.46) and multiple (95% CI 1.00–1.45) disability improvement events. Patients with EDSS scores ≥ 6 also benefited from natalizumab more than from fingolimod and had a 1.93 times higher chance (95% CI 1.11–3.34) of first disability improvement event compared with fingolimod.

3.5 Pre-Baseline Disease Activity

Patients who experienced disability worsening without relapse during the 12 months preceding study baseline tended to be slightly older and have a longer disease duration and higher EDSS score than patients who experienced relapse with or without worsening (Table 1).

The presence of a pre-baseline relapse was associated with a superior response to natalizumab. Patients from this subgroup had a lower risk of first relapse (HR 0.79; 95% CI 0.63–0.98) and a lower incidence of relapses (IRR 0.74; 95% CI 0.64–0.86) when treated with natalizumab compared with fingolimod (Fig. 2). Similarly, natalizumab tended to reduce the risk of first relapse (HR 0.67; 95% CI 0.42–1.07) and relapse incidence (IRR 0.71; 95% CI 0.43–1.17) in

comparison with fingolimod among patients who experienced disability worsening without relapse. However, we did not find unequivocal evidence in this subgroup, which was relatively small compared with the subgroup with relapses with or without disability worsening (419 vs. 3291, respectively).

A higher chance of disability improvement (HR 1.23; 95% CI 1.00–1.50) was estimated among natalizumab-treated patients who experienced pre-baseline relapse regardless of disability worsening (Fig. 3). In the relatively smaller subgroup of patients who experienced disability worsening in the absence of relapses, the effectiveness of natalizumab and fingolimod on disability improvement and worsening were comparable.

3.6 Pre-Baseline Magnetic Resonance Imaging Activity

Patients with either brain or spinal cord MRI activity captured within 12 months prior to baseline tended to be relatively younger and have a shorter disease duration and lower disability (Table 1).

Significant reduction in on-treatment relapse frequency was observed among natalizumab-treated patients in both MRI subgroups (Fig. 2). This reduction was slightly more pronounced among patients with MRI activity (IRR 0.46; 95% CI 0.35–0.61) than in those with no observed new lesions (IRR 0.62; 95% CI 0.49–0.77). This was supported by the cumulative hazard of first relapse (Fig. 2).

Natalizumab was also more effective at increasing the chance of disability improvement among patients who had

Table 4 Baseline characteristics of study subgroups in the weighted sample

Characteristics	Natalizumab				Fingolimod			
	Sex (% women)	Age, years	Disease duration, years	EDSS score	Sex (% women)	Age, years	Disease duration, years	EDSS score
Sex								
Men	–	37 ± 10.7	6.2 (2.5–12.2)	2.5 (2.0–3.5)	–	37 ± 9.7	6.3 (3.0–11.6)	2.5 (1.5–3.5)
Women	–	38 ± 10.6	7.3 (2.9–13.2)	2.5 (1.5–3.5)	–	38 ± 9.9	7.3 (3.4–12.9)	2.5 (1.5–3.5)
Age, years								
≤ 38	70	–	5.0 (2.0–8.9)	2.0 (1.5–3.0)	70	–	4.9 (2.4–8.9)	2.0 (1.5–3.0)
> 38	73	–	10.0 (4.5–16.6)	3.0 (2.0–4.0)	74	–	9.9 (5.1–16.0)	3.0 (2.0–4.0)
Disease duration, years								
≤ 7	69	34 ± 10.6	–	2.0 (1.5–3.0)	69	34 ± 9.7	–	2.0 (1.5–3.0)
> 7	74	41 ± 9.0	–	3.0 (2.0–4.0)	74	41 ± 8.7	–	3.0 (2.0–4.0)
EDSS score								
< 4	71	36 ± 10.4	6.1 (3.3–11.6)	–	72	36 ± 9.6	6.0 (2.7–10.9)	–
4–5.5	73	42 ± 10.2	10.5 (5.3–16.8)	–	73	42 ± 9.8	10.1 (6.1–16.2)	–
< 6	71	37 ± 10.5	6.7 (2.6–12.5)	–	72	37 ± 9.7	6.8 (3.1–12.0)	–
≥ 6	75	43 ± 10.8	11.0 (6.2–18.1)	–	75	44 ± 10.3	12.3 (5.9–18.1)	–
Disease activity within 12 months before BL								
Relapse with or without disability worsening	72	37 ± 10.6	6.7 (2.5–12.3)	2.5 (1.5–3.5)	72	37 ± 9.7	6.4 (2.8–12.1)	2.5 (1.5–3.5)
Disability worsening without relapse	68	39 ± 10.1	7.9 (3.8–14.4)	3.0 (2.0–4.0)	69	39 ± 9.5	8.2 (4.4–13.7)	3.0 (2.0–4.0)
None	71	41 ± 11.1	8.1 (3.7–15.5)	2.5 (1.5–3.5)	73	39 ± 10.0	7.9 (4.0–13.1)	2.0 (1.5–3.5)
MRI activity within 12 months before BL								
Not observed	84	39 ± 10.1	9.2 (5.1–15.2)	4.0 (2.0–5.0)	73	39 ± 9.8	8.8 (4.9–12.77)	2.5 (1.5–4.0)
Observed (≥ 1 new hyperintense T_2 lesion or Gd+ T_1 lesion)	72	36 ± 11.1	5.0 (1.8–9.6)	2.0 (1.5–3.0)	74	35 ± 9.6	4. 6 (2.2–9.3)	2.0 (1.5–3.5)

Data are presented as mean ± standard deviation or median (quartiles) unless otherwise indicated

BL baseline, *EDSS* Expanded Disability Status Scale, *Gd+* gadolinium enhancing, *MRI* magnetic resonance imaging

no new MRI lesion recorded during the year prior to treatment initiation (HR 1.73; 95% CI 1.19–2.51; Fig. 3).
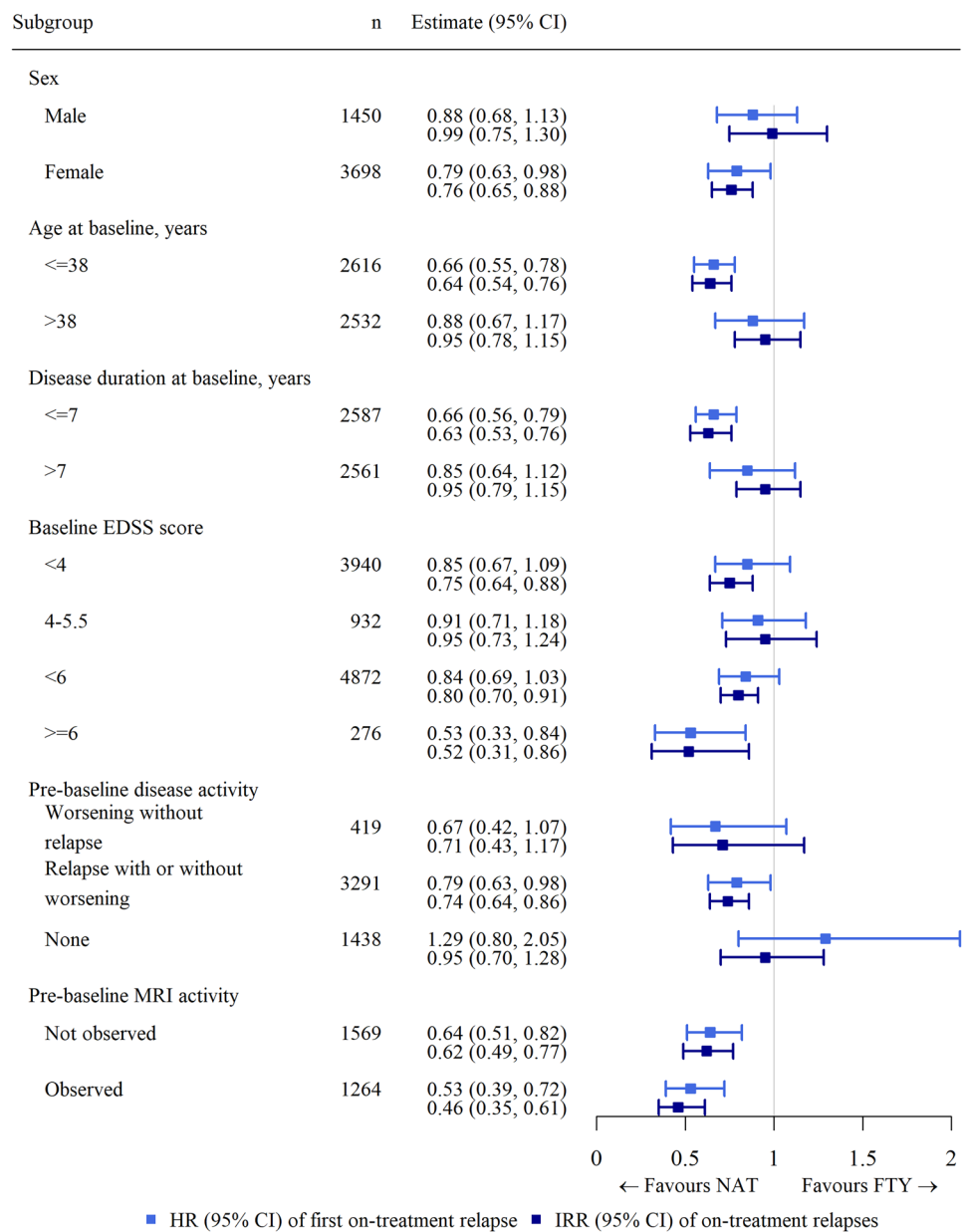
4 Discussion

We studied large cohorts from three international registries to evaluate the conditional comparative effectiveness of natalizumab and fingolimod in different subgroups of patients with RRMS. The extent to which natalizumab was associated with a superior reduction of relapses and recovery from disability when compared with fingolimod varied among different subpopulations with RRMS, and this heterogeneity was too large to be accounted for by chance alone

[21]. The observed heterogeneity was closely associated with patients' demographic and clinical characteristics. The superior effect of natalizumab on reducing relapse activity was observed mainly among women, younger patients, those with shorter disease duration, and those with pre-treatment relapses. Natalizumab was more commonly associated with disability improvement than was fingolimod, particularly among women and patients without brain or spinal cord MRI activity preceding baseline. The effectiveness of natalizumab and fingolimod on disability worsening was comparable across the subgroups [3, 4, 10, 11].

The pattern that is emerging from this and other studies indicates that the benefit from more potent therapies in reducing relapse frequency is more pronounced among
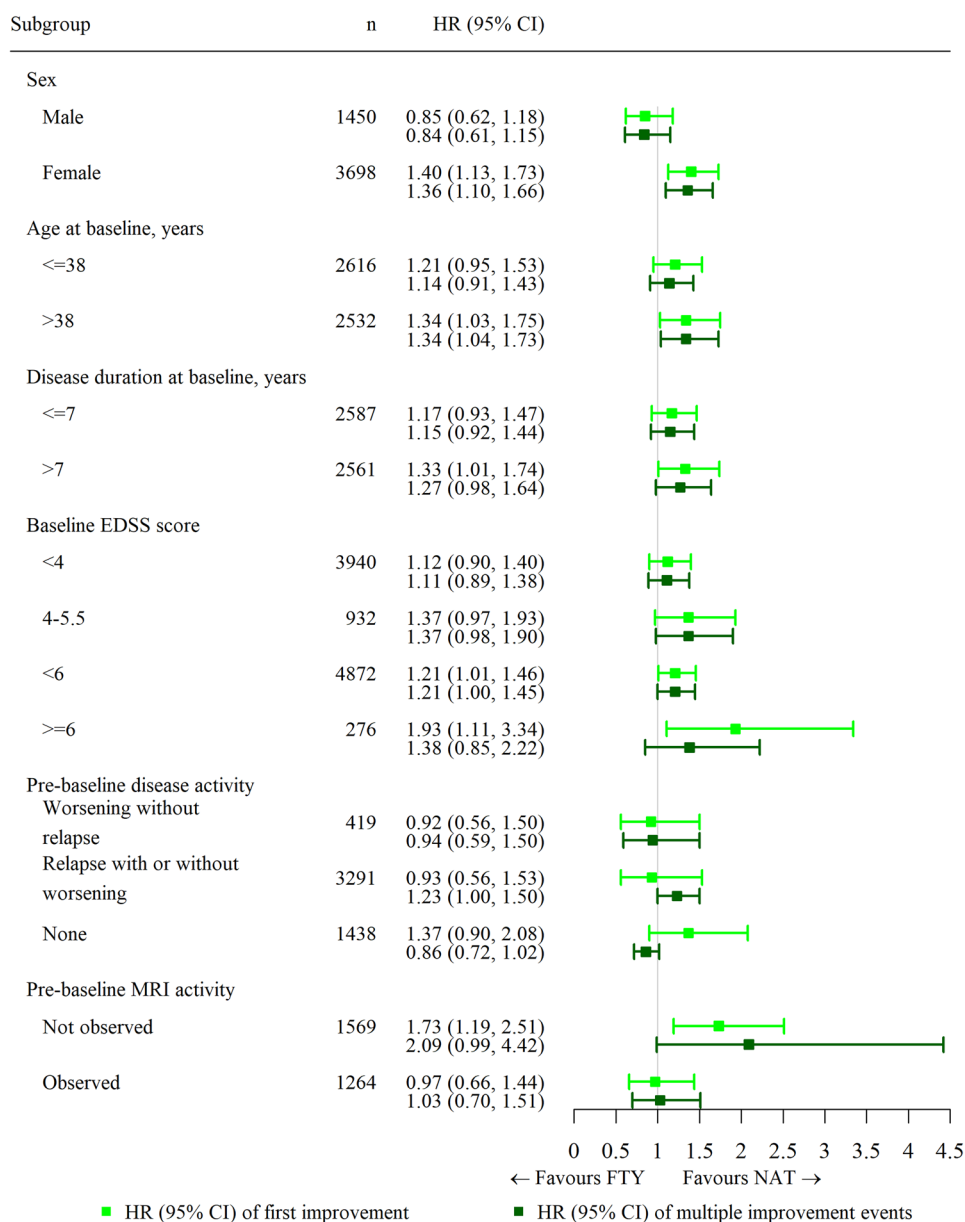
Fig. 2 Risk of relapses on natalizumab and fingolimod among subgroups. Hazard ratio (95% CI) of time to first relapse (*light blue*) and incidence rate ratio (95% CI) of on-treatment relapses (*dark blue*) in different patient subgroups. *CI* confidence interval, *EDSS* Expanded Disability Status Scale, *FTY* fingolimod, *HR* hazard ratio, *IRR* incidence rate ratio, *MRI* magnetic resonance imaging, *NAT* natalizumab

Subgroup	n	Estimate (95% CI)
Sex		
Male	1450	0.88 (0.68, 1.13)
		0.99 (0.75, 1.30)
Female	3698	0.79 (0.63, 0.98)
		0.76 (0.65, 0.88)
Age at baseline, years		
<=38	2616	0.66 (0.55, 0.78)
		0.64 (0.54, 0.76)
>38	2532	0.88 (0.67, 1.17)
		0.95 (0.78, 1.15)
Disease duration at baseline, years		
<=7	2587	0.66 (0.56, 0.79)
		0.63 (0.53, 0.76)
>7	2561	0.85 (0.64, 1.12)
		0.95 (0.79, 1.15)
Baseline EDSS score		
<4	3940	0.85 (0.67, 1.09)
		0.75 (0.64, 0.88)
4-5.5	932	0.91 (0.71, 1.18)
		0.95 (0.73, 1.24)
<6	4872	0.84 (0.69, 1.03)
		0.80 (0.70, 0.91)
>=6	276	0.53 (0.33, 0.84)
		0.52 (0.31, 0.86)
Pre-baseline disease activity		
Worsening without relapse	419	0.67 (0.42, 1.07)
		0.71 (0.43, 1.17)
Relapse with or without worsening	3291	0.79 (0.63, 0.98)
		0.74 (0.64, 0.86)
None	1438	1.29 (0.80, 2.05)
		0.95 (0.70, 1.28)
Pre-baseline MRI activity		
Not observed	1569	0.64 (0.51, 0.82)
		0.62 (0.49, 0.77)
Observed	1264	0.53 (0.39, 0.72)
		0.46 (0.35, 0.61)

← Favours NAT   Favours FTY →

■ HR (95% CI) of first on-treatment relapse   ■ IRR (95% CI) of on-treatment relapses

patients with more active disease [3, 4, 10, 22]. For instance, it is known that women tend to experience a more relapsing course of MS than men [23, 24] and that male sex is associated with a marginally poorer prognosis and lower chance of recovery than female sex [17, 25, 26]. It is therefore not surprising that natalizumab is more effective than fingolimod in preventing relapses and allowing improvement of neurological capacity in women. A previous study reported an average 17% reduction in relapse rate for every 5 years post-onset, with the exception of patients who were younger at disease onset. Patients aged < 20 years at onset had increased relapse, which peaked at 20–30 years of age [23]. In the present study, patients aged ≤ 38 years benefited more from natalizumab than from fingolimod in terms of

reduced relapse incidence. A relatively superior effect of natalizumab on relapse occurrence was also observed in the subgroup of patients with disease duration ≤ 7 years. This implies that natalizumab demonstrated the greatest potential to modify relapse rates during the early years of disease when risk of relapse is higher [24]. In the subgroup of patients with an EDSS score ≥ 6, a beneficial effect of natalizumab on relapse incidence was identified, despite the small sample size. Further, pre-baseline activity (relapse and even disability worsening) was found to be an indicator of a relatively superior response to natalizumab. This finding is consistent with previously reported subgroup analyses that demonstrated greater treatment benefits with natalizumab in patients with more active disease compared with placebo

Fig. 3 Probability of disability improvement on natalizumab and fingolimod among subgroups. Hazard ratio (95% CI) of first (*light green*) and multiple (*dark green*) 6-month confirmed disability improvements in different patient subgroups. *CI* confidence interval, *EDSS* Expanded Disability Status Scale, *FTY* fingolimod, *HR* hazard ratio, *MRI* magnetic resonance imaging, *NAT* natalizumab
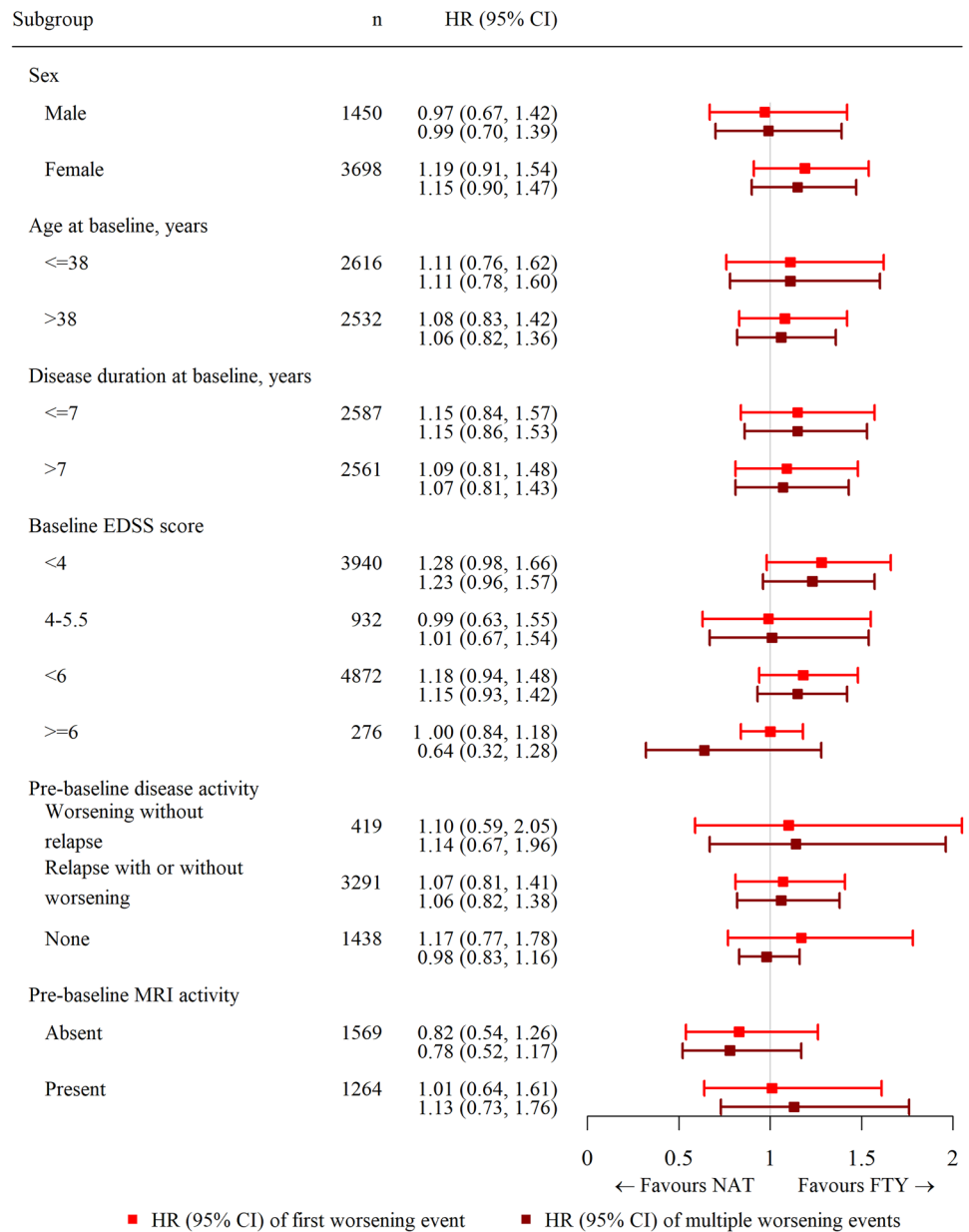
Subgroup	n	HR (95% CI)
Sex		
Male	1450	0.85 (0.62, 1.18)
		0.84 (0.61, 1.15)
Female	3698	1.40 (1.13, 1.73)
		1.36 (1.10, 1.66)
Age at baseline, years		
<=38	2616	1.21 (0.95, 1.53)
		1.14 (0.91, 1.43)
>38	2532	1.34 (1.03, 1.75)
		1.34 (1.04, 1.73)
Disease duration at baseline, years		
<=7	2587	1.17 (0.93, 1.47)
		1.15 (0.92, 1.44)
>7	2561	1.33 (1.01, 1.74)
		1.27 (0.98, 1.64)
Baseline EDSS score		
<4	3940	1.12 (0.90, 1.40)
		1.11 (0.89, 1.38)
4-5.5	932	1.37 (0.97, 1.93)
		1.37 (0.98, 1.90)
<6	4872	1.21 (1.01, 1.46)
		1.21 (1.00, 1.45)
>=6	276	1.93 (1.11, 3.34)
		1.38 (0.85, 2.22)
Pre-baseline disease activity		
Worsening without relapse	419	0.92 (0.56, 1.50)
		0.94 (0.59, 1.50)
Relapse with or without worsening	3291	0.93 (0.56, 1.53)
		1.23 (1.00, 1.50)
None	1438	1.37 (0.90, 2.08)
		0.86 (0.72, 1.02)
Pre-baseline MRI activity		
Not observed	1569	1.73 (1.19, 2.51)
		2.09 (0.99, 4.42)
Observed	1264	0.97 (0.66, 1.44)
		1.03 (0.70, 1.51)

0   0.5   1   1.5   2   2.5   3   3.5   4   4.5
← Favours FTY   Favours NAT →

■ HR (95% CI) of first improvement   ■ HR (95% CI) of multiple improvement events

[8]. Patients with no pre-baseline disease activity did not benefit more from natalizumab than from fingolimod.

Another emerging pattern suggests that natalizumab is superior to fingolimod in allowing improvement in disability status among patients with a more significant prior MS history (such as greater EDSS score and potentially also MS duration > 7 years or age > 38 years). One possible explanation for these findings is that, in patients with greater disability, potentially with a low chance of improvement [17], natalizumab being a more potent therapy than fingolimod increases the chance more than fingolimod. In the subgroup of patients with pre-baseline disability worsening but without relapses, natalizumab did not demonstrate a greater chance of recovery than fingolimod. Admittedly, the superior effect of natalizumab on disability improvement was observed in most of the groups, with only small variations in the magnitude of this effect. Of note is the increased chance of disability improvement with natalizumab versus fingolimod among the patients with no new MRI lesion recorded within the year before treatment initiation. MRI activity may herald imminent worsening of disability that could not be prevented once an MRI lesion has been established [27]. One would then expect that a relatively more potent immunotherapy would allow more effective recovery from disability among patients in whom MRI activity was not present at treatment start. In patients where MRI activity was already established before they commenced natalizumab or fingolimod, the capacity of both these therapies to reduce disability may be restricted and comparable.

Fig. 4 Risk of disability worsening on natalizumab and fingolimod among subgroups. Hazard ratio (95% CI) of first (*light red*) and multiple (*dark red*) 6-month confirmed disability worsening events in different patient subgroups. *CI* confidence interval, *EDSS* Expanded Disability Status Scale, *FTY* fingolimod, *HR* hazard ratio, *MRI* magnetic resonance imaging, *NAT* natalizumab

Subgroup	n	HR (95% CI)
Sex		
Male	1450	0.97 (0.67, 1.42)
		0.99 (0.70, 1.39)
Female	3698	1.19 (0.91, 1.54)
		1.15 (0.90, 1.47)
Age at baseline, years		
<=38	2616	1.11 (0.76, 1.62)
		1.11 (0.78, 1.60)
>38	2532	1.08 (0.83, 1.42)
		1.06 (0.82, 1.36)
Disease duration at baseline, years		
<=7	2587	1.15 (0.84, 1.57)
		1.15 (0.86, 1.53)
>7	2561	1.09 (0.81, 1.48)
		1.07 (0.81, 1.43)
Baseline EDSS score		
<4	3940	1.28 (0.98, 1.66)
		1.23 (0.96, 1.57)
4-5.5	932	0.99 (0.63, 1.55)
		1.01 (0.67, 1.54)
<6	4872	1.18 (0.94, 1.48)
		1.15 (0.93, 1.42)
>=6	276	1 .00 (0.84, 1.18)
		0.64 (0.32, 1.28)
Pre-baseline disease activity		
Worsening without relapse	419	1.10 (0.59, 2.05)
		1.14 (0.67, 1.96)
Relapse with or without worsening	3291	1.07 (0.81, 1.41)
		1.06 (0.82, 1.38)
None	1438	1.17 (0.77, 1.78)
		0.98 (0.83, 1.16)
Pre-baseline MRI activity		
Absent	1569	0.82 (0.54, 1.26)
		0.78 (0.52, 1.17)
Present	1264	1.01 (0.64, 1.61)
		1.13 (0.73, 1.76)

← Favours NAT   Favours FTY →

■ HR (95% CI) of first worsening event   ■ HR (95% CI) of multiple worsening events

On the other hand, where the disease was previously radiologically stable, natalizumab may exert a superior effect on reducing further inflammation within the central nervous system than fingolimod, thus allowing more efficient recovery of neurological function. Taken together, these observations suggest that natalizumab may allow a more complete recovery of function in patients with less functional reserve [28].

Finally, in keeping with all previously published studies, the capacity of natalizumab and fingolimod to reduce the risk of disability worsening was comparable [3, 4, 10]. This observation was homogenous across the studied subgroups, suggesting that the protection from future inflammation that results in permanent disabiltiy is modulated similarly by the two compared agents.

The lack of randomization in treatment allocation may have introduced bias in estimates of treatment effects. We addressed this limitation by implementing a rigorous statistical approach where each study patient was weighted using IPTW based on propensity score. The propensity score model ensured the balance between treatment groups on measured covariates. However, the propensity score matching did not adjust for unknown confounders. Although the propensity score model included all relevant available covariates, stratification into subgroups was univariate. Therefore, we refrained from making comparisons of the relative treatment effectiveness of natalizumab and fingolimod across subgroups and instead focused on emphasizing patient groups in which the identified difference between the two

therapies was most pronounced. The MRI data were limited and only available in the MSBase and OFSEP databases. Emerging complementary biomarkers, such as serum neurofilament light concentration, may improve comparability of data originating from multiple diverse sources [29]. Also, no data for safety of the studied treatments and the risk of progressive multifocal leukoencephalopathy were included.

5 Conclusions

This subgroup analysis indicated that natalizumab was associated with lower relapse frequency than fingolimod among patients with more clinically active MS. It was also associated with a higher chance of improvement of disability in most patients, particularly those with more significant prior MS history. The effect of the two therapies in reducing confirmed disability worsening was similar across subgroups. These observations confirm that different groups of patients derive differing benefits from MS therapies. Therefore, both clinicians and their patients should consider the patient's demographic and clinical characteristics, such as sex, age, disease duration and prior clinical and radiological disease activity, when making decisions about specific therapeutic agents.

Declarations

Consent for publication Not applicable.

Availability of data and material MSBase is a data processor and warehouses data from individual principal investigators who agree to share their datasets on a project-by-project basis. Each principal investigator will need to be approached individually for permission to access the datasets. The OFSEP data can be obtained upon request after evaluation by the OFSEP scientific committee and validation from the OFSEP steering committee. Details can be found on http://www.ofsep.org/en/data-access. Data from DMSR will be shared upon request from a qualified investigator under approval from the Danish Data Protection Agency and the board of the Danish Multiple Sclerosis Group.

Code availability Available upon request.

Authors' contributions SS, ML, and JBA contributed to the design of the study, conducted and interpreted the analysis, and drafted, revised, and approved the manuscript. MM, SV, HB, and TK conceptualized and designed the study, contributed to data acquisition, interpreted the results, and revised and approved the manuscript. EL, RC, and DL contributed to the design of the study, interpreted the results, and revised and approved the manuscript. DH, EKH, RA, GI, SO, FP, MO, AL, MT, PG, FGM, BY, AP, MG, PD, CB, MT, PM, MS, JLS, RT, PS, DF, FG, JP, DM, OS, KB, AVW, BVW, TC, DS, SV, MD, GE, JC, AR, JDS, EM, HZ, PL, GD, CLF, TM, EB, PC, JP, BS, OG, ET, OH, AAK, BB, OC, PC, AM, AW, JPC, AM, IP, KH, CP, NM, CL, CN, NKH, FTS, PSS, CCP, PVR, MBJ, JLF, SB, HKM, and KIS contributed substantially to data acquisition and interpretation of the analysis, and revised and approved the manuscript. SS, ML, and JBA contributed equally. MM, SV, HB, and TK contributed equally. All authors approved the final version of the manuscript for submission and publication and thus assume responsibility for the work presented in the manuscript.

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