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ORIGINAL COMMUNICATION

Switching from natalizumab to fingolimod treatment in multiple sclerosis: real life data from the Austrian MS Treatment Registry

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Abstract

Objectives To compare the efficacy of natalizumab (NTZ) and fingolimod (FTY) in the treatment of relapsing–remitting multiple sclerosis (MS) in sequential use in common and as a function of transition periods in a nationwide observational cohort using prospectively collected data from a real-life setting.

Materials and methods We included 195 patients from the Austrian MS Treatment Registry, who had started treatment with NTZ at any time since 2006 and stayed on NTZ for at least 24 months, switched afterwards within 1 year to FTY and stayed on FTY for at least another 12 months. Transition periods between NTZ and FTY were grouped into three different intervals: < 3 months (135 patients), 3–6 months (44 patients), and 6–12 months (16 patients).

Results Estimated mean annualized relapse rates (ARR) over a mean treatment period of 44 months were 0.26 for NTZ and 0.32 for FTY ($p = 0.381$) over 46 months. In the treatment gap, differences were found concerning the relapse probability, seven (5.2%) patients in the < 3 months group, six (13.6%) in thef 3–6 months group, and seven (43.8%) in the 6–12 months group ($p < 0.001$). After this treatment gap, no significant differences concerning ARR, EDSS change, EDSS progression, and regression were observed regardless the proceeding transition periods. Significantly higher efficacy of NTZ compared to FTY in sequential use was found regarding EDSS change, EDSS progression, and EDSS regression sustained for 12 and 24 weeks.

Conclusions First, we here show an increased short-time risk for relapses during the treatment gap between NTZ and FTY therapy, dependent on the length of transition time. Second, the disease course after switching to FTY remained stable in the long-term evaluation. Therefore, switching from NTZ to FTY in a real-world setting appears efficacious and safe, but this data advocate for a short switching gap of 3 months or less.

Keywords Multiple sclerosis · Natalizumab · Fingolimod · Switch

Introduction

High treatment efficacy of natalizumab (NTZ) and fingolimod (FTY) for relapsing–remitting multiple sclerosis (RRMS) has been proven in randomized trials [1–3]. In comparison to placebo groups, NTZ reduced the annualized relapse rate (ARR) by 68% [1] and FTY by 48–55% [2, 3]. In addition, FTY showed a reduction of the ARR by 52% versus interferon beta-1a [4]. However, clinical efficacy is difficult to compare directly from these pivotal trials because the ARR in the placebo arms was considerably different, namely 0.81 in the NTZ [1] and 0.40 in the FTY studies [2, 3].

However, the use of NTZ is associated with a risk for John-Cunningham virus (JCV)-induced progressive

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multifocal leukoencephalopathy (PML), which increases with anti-JCV antibody positivity and duration/doses of NTZ treatment. Therefore, NTZ treatment discontinuation is considered for JCV seropositive patients who had been treated with NTZ for over 24 months [5]. On the other hand, there is evidence of reappearing disease activity after NTZ cessation demanding a sequential treatment with other disease-modifying drugs [6, 7]. FTY is an appropriate alternative for this treatment switch [8–16].

Discrepancies were observed in studies regarding the clinical course after switching from NTZ to FTY. Some studies [8–11] showed a reactivation of disease activity after the treatment switch to FTY, whereas other studies did not observe re-occurrence of relapse activity during FTY treatment [12–14]. A shorter transition time from NTZ to FTY is considered beneficial and safe [15, 16].

These discrepancies ask for further investigations to confirm or rebut published findings.

The objective of our study was to compare the efficacy of NTZ and FTY treatment, first, in sequential use in common and, second, as a function of transition periods, in a nationwide observational cohort using data collected prospectively in a real-life setting.

Materials and methods

Data collection

The Austrian MS Treatment Registry (AMSTR), [17] established in 2006 to maintain quality control and to comply with reimbursement regulations of the Austrian sick funds, allows to obtain clinical data, to assess indications and the clinical profiles of the treated patients, and to monitor safety in real life. The AMSTR is part of the dense network of MS centres in Austria, which is constituted by MS clinics from neurological departments and some dedicated neurological practices that have been assigned this status by the Austrian Society of Neurology based on defined quality criteria. In addition, prescriptions of DMTs for MS are exclusively reserved for MS centers. Thus, prescriptions and treatment documentations are evenly distributed across Austria. The AMSTR is compliant with Austrian laws on bioethics and it was also approved by the ethical committee of the Medical University of Vienna (EC number 2096/2013).

AMSTR documents anonymous baseline data, including the date of clinical onset of MS and disease duration, relapses in the prior 12 months, EDSS, gross MRI activity, and previous disease-modifying therapies (DMT). Follow-up data (relapses, EDSS, adverse events [AEs], change or discontinuation of treatment) are required to be documented every 3–6 months. Each relapse had to be confirmed by a neurologist at the MS centre and documented in the AMSTR. Documentation requires relapse onset, EDSS, and use/dose of i.v. methylprednisolone treatment. Besides the fact that applying the AMSTR is mandatory for reimbursement, a special quality-related feature of the AMSTR is an external and independent data monitoring to improve data acquisition, input, and management in terms of completeness and plausibility of documented data.

In 2011, the European Medicines Agency (EMA) approved FTY along the same indication criteria as NTZ. Reimbursement for NTZ and FTY in Austria adheres to this approval. Thus, NTZ- and FTY-treated patients in Austria had to have either at least one relapse in the prior 12 months despite treatment with interferon beta or glatiramer acetate and at least nine T2 lesions or at least one gadolinium-enhancing lesion on recent brain MRI ("indication A"), or two or more severe relapses in the preceding treatment-naïve 12 months and one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI ("indication B").

We investigated a cohort of 195 patients from the AMSTR, who started treatment with NTZ at any time since 2006 and stayed on treatment with NTZ for at least 24 months. Transition periods between NTZ and FTY had to be no longer than 12 months and were grouped into three different periods: < 3 months, 3–6 months, and 6–12 months. After switching to FTY treatment, duration of this treatment had to last for at least 12 months.

The primary outcome measure was the ARR under treatment with NTZ and FTY and during the transition period. Relapses were defined as new or worsening neurological symptoms lasting for at least 24 h in the absence of fever.

Further outcome measures were the total number of relapses, EDSS progression or regression confirmed after 3 and 6 months, and EDSS changes during treatment (difference between EDSS at the last visit and at the baseline). Sustained disability progression or regression was defined as an increase or decrease from the baseline of at least 1.0 point in the EDSS score (or at least 0.5 points for patients with a baseline EDSS score greater than 5.5) that persisted for at least 12 or 24 weeks.

For analyses of the treatment interruption of FTY, three causes were defined, i.e., (1) permanent treatment interruption (2) transient treatment interruption and re-start with FTY, and (3) treatment interruption and re-start with any new medication.

Statistical methods

Results of statistical testing were considered as statistically significant for nominal p values not exceeding a significance level of alpha = 0.05. No corrections for multiple testing were performed. Consecutive treatment periods were compared using Wilcoxon signed ranks test for quantitative

characteristics and McNemar test for categorical characteristics, respectively. Kaplan–Meier estimators were used to derive survival functions for time to event data. Log-rank test was used to compare survival distributions between transition period subgroups. Chi-square test and Kruskal–Wallis test were used to compare transition period subgroups for categorical characteristics and quantitative characteristics, respectively.

As statistical programmes, we used IBM SPSS Statistics for Windows, Version 24.0 (Armonk, NY: IBM Corp.) and BiAS for Windows, Version 11.08 (epsilon Verlag, Klinikum der Goethe-Universität Frankfurt, Germany).

Results

According to the inclusion criteria stated above, 195 RRMS patients were included in this study for further analyses. Their demographic and descriptive clinical data are shown in Table 1.

Regarding the first objective to compare the efficacy of NTZ and FTY in a sequential use, the mean treatment periods for the 195 RRMS patients were 44 (SD: 17) months for NTZ and 46 (SD: 22) months for FTY. Eighty (41%) patients treated with NTZ and 81 (41.5%) patients treated with FTY experienced a relapse during the observation period, which accounts for mean annualized relapse rates (ARR) of 0.26 (SD: 0.46) for NTZ and 0.32 (SD: 0.53) for FTY ($p = 0.381$).

With regard to the transition period, 135 patients switched within < 3 months (mean 1.6 months, SD: 0.87), 44 within 3–6 months (mean 4.2 months, SD: 0.99), and only 16 within 6–12 months (mean 6.8 months, SD: 0.68). The baseline data of these 195 patients showed no significant imbalances (Table 1).

The mean transition time between the two drugs was 2.6 months (SD: 1.9) and 20 persons (10.3%) experienced a relapse during this period. Differences were found concerning the frequency of relapses in the different treatment gaps: seven (5.2%) patients in the < 3 months group, six (13.6%) in the 3–6 months group, and seven (43.8%) in the > 6–12 months group ($p < 0.001$) (Fig. 1). This observation was independent from the NTZ treatment duration before switching (data not shown).

However, after having switched from NTZ to FTY—independent from the transition time—no significant differences regarding the probability to experience a relapse within the first 3 months of FTY treatment ($p = 0.840$) were noted. In addition, the transition time, including the occurrence of relapses within the transition time, had no significant impact on the further disease activity. Specifically, the ARR for FTY-treated patients did not significantly differ regardless the proceeding transition periods, namely 0.31 (SD: 0.6) within < 3 months, 0.36 (SD: 0.5) within 3–6 months, and 0.24 (SD: 0.45) within 6–12 months ($p = 0.304$).

Table 1 Baseline patient characteristics at natalizumab start

	< 3 months $N = 135$	3–6 months $N = 44$	6–12 months $N = 16$	All $N = 195$
Female[b]				
N	86	25	10	121
%	63.7%	56.8%	62.5%	62.1%
Age[a]				
Mean	35.0	34.2	37.6	35.0
SD	9.0	8.6	9.1	8.9
Duration of MS at baseline (years)[a]				
Mean	7.5	8.8	10.6	8.0
SD	5.8	7.1	6.9	6.2
EDSS at baseline[a]				
Mean	*3.0*	*3.0*	*3.2*	*3.0*
SD	*1.4*	*1.6*	*1.7*	*1.5*
Relapse rate within 12 months prior to treatment start[a]				
Mean	2.5	2.2	2.2	2.4
SD	1.2	1.2	1.2	1.2
Prior treatment[b]				
Yes				
N	121	42	13	176
%	89.6%	95.5%	81.3%	90.3%
Indication[bc]				
A				
N	108	35	9	152
%	80.6%	79.5%	60%	78.8%
B				
N	26	9	6	41
%	19.4	20.5%	40%	21.2%
> 9 T2 lesions[b]				
Yes				
	126	41	15	182
	95.5	100%	100%	96.8%
Gd-enhancing lesions[b]				
Yes				
	85	25	12	122
	66.9%	65.8%	80%	67.8%

MRI data were not known for all patients

ARR annualized relapse rate, *EDSS* Expanded Disability Status Scale, *SD* standard deviation

[a]Comparison using Kruskal–Wallis test revealed no significant difference

[b]Comparison using Chi-Quadrat test revealed no significant difference

[c]Indication A = at least one relapse in the prior 12 months despite the treatment with either interferon beta or glatiramer acetate; indication B = at least two severe relapses in the prior 12 months in treatment-naive patients

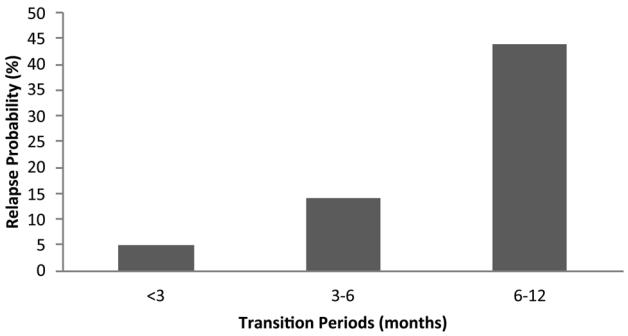

Fig. 1 Cumulative frequency for experiencing a relapse within the transition period

Mean EDSS change during NTZ therapy was − 0.12 (= improvement, SD: 1.04) versus 0.36 (= worsening, SD: 0.97) during FTY treatment ($p < 0.001$).

Significant differences were found regarding the occurrence of sustained EDSS progression, which was lower in NTZ compared to FTY, both for 12 weeks (Figs. 2a, b; 9.2% versus 18.5%, $p = 0.010$) and 24 weeks data (8.2% versus 16.4%, $p = 0.020$). No significant differences were observed concerning sustained EDSS progression for 12 weeks and 24 weeks during FTY treatment between the three subgroups ($p = 0.389$ and $p = 0.249$).

When analyzing sustained EDSS regression for 12 and 24 weeks by comparing NTZ and FTY, significant differences were observed, with higher rates in NTZ treated patients (16.9% versus 7.2% for 12 weeks, $p = 0.007$ (Figs. 3a, b) and 14.9% versus 7.2% for 24 weeks ($p = 0.028$). Once again no significant relation between EDSS regression for 12 and 24 weeks and the duration of the treatment gap was found ($p = 0.784$ and $p = 0.784$).

The reasons for switching from NTZ to FTY were mainly serological presence of JCV antibodies and the NTZ treatment duration being longer than 2 years ($n = 132$), other infrequent reasons included disease progression (clinical and/or radiological activity) ($n = 69$), patient's wish ($n = 66$) and adverse events (AEs) ($n = 4$). Note that treating neurologists could name several reasons per patient.

52 (26.7%) patients interrupted FTY treatment, with 31 stoppings, 6 pausings and 15 switching therapy. Six patients switched from FTY to dimethylfumarate (40%), five to alemtuzumab (33.4%), two to ocrelizumab (13.3%), one to teriflunomide (6.6%), and one back to NTZ (6.6%).

The reasons for interrupting FTY were mainly disease progression ($n = 39$), patient's wish ($n = 24$), AEs ($n = 16$), and pregnancy or the wishes to conceive ($n = 5$). No case of progressive multifocal leukoencephalopathy (PML) occurred in our study population.

Discussion

Previous studies showed an effect between the length of NTZ to FTY treatment gap and disease activity. Transition times of 3 months or less were associated with better outcomes [8–16].

Relapses occurred soon after cessation of NTZ and decreased within the first year of the FTY treatment. This is in line with previous studies showing a mean period from NTZ discontinuation to occurrence of disease activity of 4 months, occurring as early as less than 8 weeks [6, 18]. We observed less relapses during the 3–6 months transition period, namely 13.6% versus 30% in other studies [8, 15]. One likely explanation is that we only included patients staying on FTY therapy for at least 12 months. Thus, 12

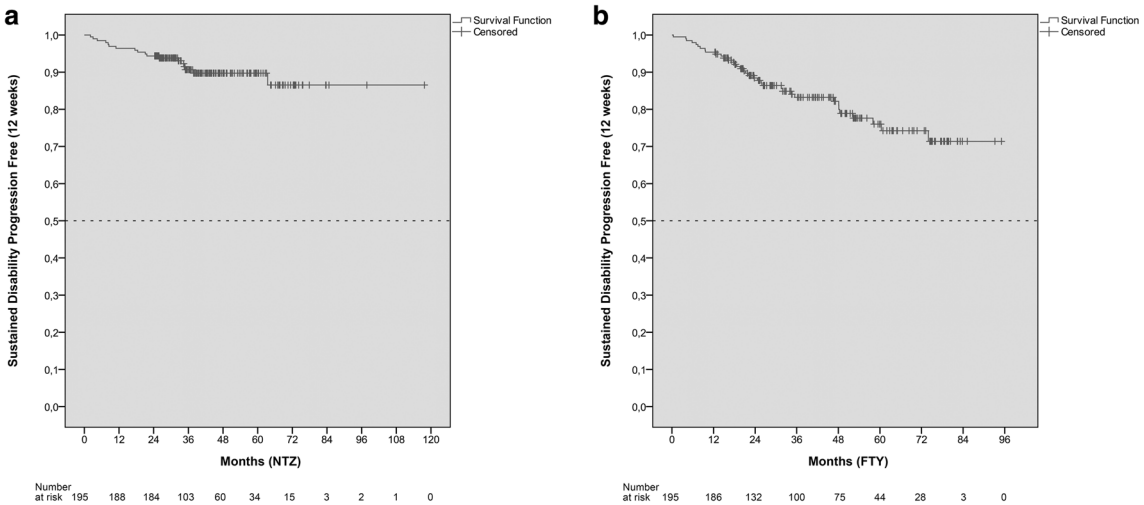

Fig. 2 Sustained disability progression free for 12 weeks with (**a**) natalizumab and (**b**) fingolimod. *NTZ* natalizumab, *FTY* fingolimod

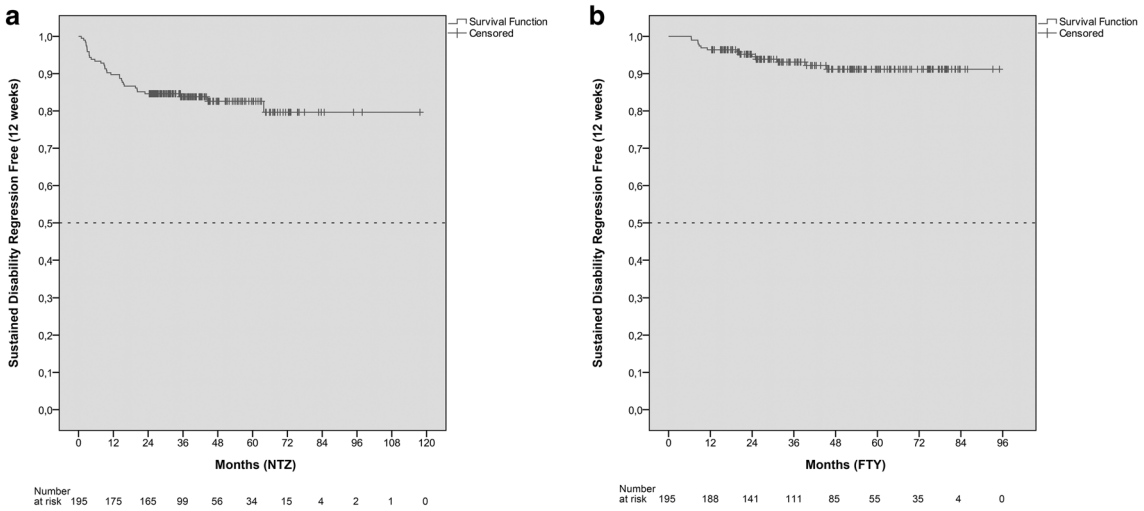

Fig. 3 Sustained disability regression free for 12 weeks with (**a**) natalizumab and (**b**) fingolimod. *NTZ* natalizumab, *FTY* fingolimod

patients (6%) with less than 12 months on FTY therapy were excluded, but this had a negligible impact on our results.

We did not find any significant differences regarding ARR, EDSS change, EDSS progression, and regression during FTY treatment comparing the three transition time cohorts, in line with previous reports [15, 16]. In contrast to the mentioned studies, the observation period in our cohort under FTY and NTZ treatment, respectively, 44 and 46 months, was much longer resulting in more robust long-time data. For some baseline variables, the 6–12 months transition cohort seems to differ quite clearly from one of the other two groups (e.g., duration of MS) and no statistically significant group effect was observed. As this group is rather small, this seems to be the reason for no statistical significance, and therefore overseeing a group effect appears possible. But as all groups together were investigated in an overall test using the full sample size of the study population, too small sample size seems to be a minor problem here. Lacking significance follows rather from too high variability compared to the observed group differences.

In addition, we observed a significantly higher impact of NTZ on EDSS change ($p < 0.001$), EDSS progression sustained for 3 and 6 months ($p = 0.010$ and $p = 0.020$), and EDSS regression sustained for 3 and 6 months ($p = 0.007$ and $p = 0.028$), comparing the sequential use of NTZ and FTY irrespective of the length of the treatment gap. Diem et al. analyzing NEDA-3 also described superior efficacy for NTZ versus FTY in sequential use in the long-term evaluation [9]. EDSS worsening during fingolimod treatment could also reflect an age-related aspect, because a mean delay of nearly 47 months between NTZ and FTY start was observed.

The reasons for interrupting FTY in our cohort were mainly disease progression ($n = 39$), patient's wish ($n = 24$), and AEs ($n = 16$). This is in contrast to Vollmer et al., where the majority of discontinuations were due to adverse events [15]. Comparable with Vollmer et al., no cases of PML occurred in our cohort, in contrast to Giovannoni et al. [19].

The strengths of our study are that this work represents data from a nationwide observational study comprising patients in Austria who have been treated with NTZ and followed by FTY since 2006. The AMSTR is a secure web-based platform, which enables treating neurologists in all Austrian MS centres to perform immediate online documentation during patient visits. To ensure high documentation and data quality in terms of completeness and plausibility, the AMSTR is monitored by an external and independent clinical research organization.

There are also limitations to our study. One limitation concerns the missing information on MRI findings during the observational period. MRI data were only available at baseline before starting treatment with NTZ. Another aspect refers to the fact that differences in the treatment-free intervals might have been caused by factors influencing the treating neurologist´s decision such as less active disease, but on the other hand, this reflects real-life situations, and therefore is an intrinsic limitation of such studies.

In conclusion, our results showed, on the one hand, an increased short-time risk for experiencing a relapse during the treatment gap between NTZ and FTY therapy which is dependent on the length of transition time, and on the other hand, a stable disease course after switching to FTY in the long-term evaluation. In summary, switching from NTZ to FTY in a real-world setting is efficacious and safe, but our results advocate for a short switching gap of 3 months or less.

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Compliance with ethical standards

Conflicts of interest Michael Guger received support and honoraria for research, consultation, lectures, and education from Almirall, Bayer, Biogen, Celgene, Genzyme, MedDay, Merck, Novartis, Octapharma, Roche, Sanofi Aventis, Shire, and TEVA ratiopharm. Christian Enzinger received funding for travel and speaker honoraria from Biogen, Bayer, Celgene, Merck, Novartis, Roche, Shire, Sanofi-Genzyme, and Teva Pharmaceutical Industries Ltd./sanofi-aventis, research support from Merck Serono, Biogen, Sanofi-Genzyme, and Teva Pharmaceutical Industries Ltd./sanofi-aventis and serving on scientific advisory boards for Bayer Schering, Biogen, Merck Serono, Novartis, Roche, and Teva Pharmaceutical Industries Ltd./sanofi-aventis. Fritz Leutmezer has received funding for travel and speaker honoraria from Biogen, Bayer Schering Pharma, Merck Serono, Novartis, Genzyme, Santhera, and Teva Pharmaceutical Industries Ltd./sanofi-aventis. Jörg Kraus received consulting and/or research funding and/or educational support from Almirall, Bayer, Biogen, Celgene, MedDay, Medtronic, Merck, Novartis, Roche, Sanofi-Aventis, Shire, TEVA ratiopharm. Stefan Kalcher declares that there is no conflict of interest. Erich Kvas declares that there is no conflict of interest. Thomas Berger has participated in meetings sponsored by and received honoraria (lectures, advisory boards, consultations) from pharmaceutical companies marketing treatments for multiple sclerosis: Almirall, Bayer, Biogen, Biologix, Bionorica, Genzyme, MedDay, Merck, Novartis, Octapharma, Roche, Sanofi/Genzyme, TG Pharmaceuticals, TEVA-ratiopharm, and UCB. His institution has received financial support in the last 12 months by unrestricted research grants (Biogen, Bayer, Merck, Novartis, Sanofi/Genzyme, and TEVA ratiopharm) and for participation in clinical trials in multiple sclerosis sponsored by Alexion, Bayer, Biogen, Merck, Novartis, Octapharma, Roche, Sanofi/Genzyme, and TEVA.

Ethical standards The AMSTR is compliant with Austrian laws on bioethics and it was also approved by the ethical committee of the Medical University of Vienna (EC number 2096/2013).

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