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Research Paper

Predictors for multiple sclerosis relapses after switching from natalizumab to fingolimod

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Abstract

Background: Risks of natalizumab (NAT) therapy have to be weighed against disease recurrence after stopping NAT.

Objectives: The objective of this paper is to identify risk factors for recurrence of relapses after switching from NAT to fingolimod (FTY) in relapsing–remitting multiple sclerosis (RRMS).

Methods: Patients (n = 33) were treated with NAT for ≥1 year, and then switched to FTY within 24 weeks (mean follow-up on FTY 81.1 (SD 26.5) weeks). Annual relapse rates (ARR) and Expanded Disability Status Scale scores (EDSS) were assessed. Descriptive statistics, univariate logistic regression analysis, and receiver operating characteristic curves were conducted.

Results: Overall, 20 patients (61%) had relapses after discontinuation of NAT and 16 (48%) during FTY therapy. The maximum incidence of relapses occurred between weeks 13–24 post-NAT. The last EDSS during the switching period predicted relapses during subsequent FTY therapy. EDSS >3 separated most powerfully between the groups (sensitivity 64%, specificity 88%) and significantly predicted relapses (relative risk 3.27, 95% CI: 1.5–7.3). Seventy-five percent of patients with EDSS ≤ 3 remained free of relapses, compared to 18% of patients with EDSS >3.

Conclusions: There was an increase of the ARR in the first year after switching from NAT to FTY. Last EDSS during the switching period was a predictor of relapses during FTY.

Keywords: Multiple sclerosis, natalizumab, fingolimod, disease activity, EDSS, predictor

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Introduction

Natalizumab (NAT) is approved for treatment of relapsing–remitting multiple sclerosis (RRMS).[1,2] The major risk of long-term therapy is progressive multifocal leukoencephalopathy (PML), caused by the John Cunningham virus (JCV).[3] According to the current risk stratification scheme, JCV antibody positivity, NAT treatment >2 years, and immunosuppressive pretreatment increase PML risk. Particularly JCV antibody-positive patients with at least one additional risk factor are at a high PML risk.[4] As a consequence these patients often choose to discontinue NAT therapy. Unfortunately, disease activity usually returns to pre-NAT levels within months after NAT withdrawal.[5] Several strategies have been applied to prevent the recurrence of relapses after cessation of NAT.[6] Of those, intravenous (IV) methylprednisolone bridging[7,8] and switching to interferon beta (IFN)[9,10] or glatiramer acetate (GLAT)[11] do not seem to be sufficiently effective. Hence, switching to fingolimod (FTY) is often preferred. In retrospective observations and cohort studies FTY was more efficacious than "drug holidays" or IFN and GLAT in preventing the recurrence of disease activity within the first six to nine months of treatment.[6] Still, around half of FTY-treated patients experienced relapses after NAT discontinuation, mostly during the switching period or the first weeks of treatment. The length of the time interval between discontinuation of NAT and start of FTY seemed to affect disease activity.[12] Until now it has not been well established which treatment strategy should be followed after cessation of NAT and which parameters might predict a higher risk of relapses.

We followed up and extended our cohort of patients switched from NAT to FTY.[12] Compared to our previous report, we now focused on those NAT-treated patients who were treated for at least 12 months with NAT, switched to FTY within 24 weeks after NAT discontinuation, and were followed up for at least 12 months on subsequent FTY treatment. Additionally, we used logistic regression analysis to identify clinical risk factors, which might help to predict response to FTY after NAT withdrawal.

Methods

This retrospective observational study was conducted at three university-based tertiary referral MS centers. Electronic databases were searched for MS patients who had been switched from NAT to FTY and charts reviewed for the following inclusion criteria: diagnosis of RRMS according to revised McDonald criteria,[13] at least 12 months of NAT therapy, switching from NAT to FTY within 24 weeks, and follow-up for at least 12 months after start of FTY. We identified a total of 39 patients. Six patients had to be excluded because of a switching period >24 weeks or a follow-up during FTY <12 months. All patients were continuously monitored by regular outpatient visits every three to six months. Compared to our previous report,[12] we included a larger patient population and an extended time of NAT therapy and follow-up during FTY treatment. Nineteen patients of the present observation had already been included in the preceding observation.[12]

NAT had been administered every 4.2 (SD 0.6) weeks and all patients were negative for neutralizing anti-NAT-antibodies. Medical records were assessed for disease course, previous therapies, relapses before, during and after NAT therapy and disability scored by the Expanded Disability Status Scale (EDSS), which is routinely performed in all participating centers. Relapses were defined by standard criteria as confirmed clinical deterioration of at least 24 h duration. A magnetic resonance imaging (MRI) scan was obtained if there was any doubt contradicting the existence of an MS relapse. Relapses were treated with 1 g methylprednisolone IV for three to five days. The annualized relapse rate (ARR) was calculated for different periods by dividing the total number of relapses by the duration of that period in years.

To identify potential predictors of the response to FTY, the following variables were analyzed for their influence on relapses during FTY by univariate logistic regression analysis and for a significantly different distribution in patients with and without relapse during FTY by Mann-Whitney-Exact Test: ARR prior to NAT, ARR during NAT, ARR during switching period, EDSS at start of NAT, last EDSS during NAT, and last EDSS during the switching period (cessation of NAT until start of FTY). To determine the cut-offs separating most powerfully (assumption of an equal importance of sensitivity and specificity) between patients with and without relapse during FTY, receiver operating characteristic curves (ROCs) were carried out for all previously identified differently distributed variables. The predictive value of the determined cut-offs on ARR during FTY in all patients and in the subgroup of patients who were relapse free during NAT treatment was analyzed.

Mann-Whitney-Exact, Fisher's-Exact, Wilcoxon signed-rank test, and univariate logistic regression analysis were calculated using SPSS 20. This investigation was approved by the institutional ethics committee of the Ruhr University Bochum.

Results

Thirty-three RRMS patients were included in the analysis (Table 1). NAT was discontinued because of perceived risk of PML (n = 28; duration of NAT ≥24 months 22/28, JCV antibody positive 16/28, immunosuppressive pre-treatment 6/28), availability of the oral agent FTY (n = 3), or treatment failure of NAT (n = 2). The mean ARR at baseline prior to NAT was 2.5 (SD 1.3). During NAT and FTY treatment, the ARR was significantly reduced compared to the baseline ARR (mean ARR NAT 0.2 (SD 0.5), FTY 0.7 (SD 1.6)), indicating that both NAT and FTY suppressed clinical disease activity in this cohort (Figure 1).

After cessation of NAT a significant increase of disease activity occurred, regardless of whether the switching period was included in the analysis or not (mean ARR switching period 0.67 (SD 1.6), total post-NAT 0.64 (SD 0.83), FTY 0.7 (SD 1.6)). Overall, 61% of patients (20/33) had relapses after cessation of NAT and 48% (16/33) during FTY, of whom 63% (10/16) had been relapse free during NAT and 87.5% (14/16) during the switching period. All patients with relapses during NAT also had relapses in the switching period or while on FTY treatment. Although two patients had an increase of >1.0 EDSS points after NAT withdrawal, there were neither "catastrophic" relapses on FTY nor a significant deterioration of EDSS after cessation of NAT at the group level (Table 1). The maximum relapse activity occurred between weeks 13 and 24 after NAT discontinuation and considerably dropped after week 37.

Table 1. Clinical characteristics of patients (shown are mean and standard deviation (SD) or median and interquartile range (IQR)).

	All patients (n = 33)
Gender (female)	61% (20/33)
Age at onset of NAT (years)	35.6 (SD 10.5)
Disease duration prior NAT (years)	7.5 (SD 6.1)
Duration of NAT therapy (months)	33.5 (SD 14.7)
Number of NAT infusions	31.8 (SD 12.7)
Therapy-free episode (weeks)	14.9 (SD 4.7)
Duration of FTY therapy (weeks)	81.1 (SD 26.5)
ARR prior to NAT[a]	2.0 (IQR 1.62) (n = 30)
ARR during NAT	0 (IQR 0.1)
ARR during switching period[b]	0 (IQR 0)
ARR during FTY	0 (IQR 1.0)
ARR total post-NAT[c]	0.4 (IQR 1.3)
EDSS at start of NAT	3.1 (SD 1.5) (n = 29)
Last EDSS during NAT[d]	3.0 (SD 1.6) (n = 31)
Last EDSS during switching period	3.2 (SD 1.6) (n = 31)
Last EDSS during FTY	3.3 (SD 1.7) (n = 32)

NAT: natalizumab; ARR: annual relapse rates; FTY: fingolimod; EDSS: Expanded Disability Status Scale. [a]Last year prior to NAT. [b]Extrapolated to one year. [c]Switching period + time on FTY. [d]Evaluated during last year of NAT therapy.

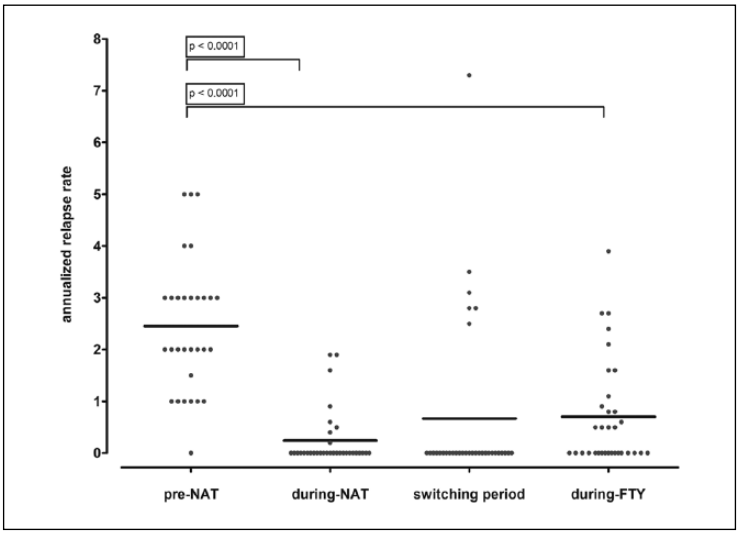

Figure 1. Comparison of the annualized relapse rate (ARR) for 33 relapsing–remitting multiple sclerosis (RRMS) patients switched within 24 weeks from natalizumab (NAT) to fingolimod (FTY).
Pre-NAT is the time one year before NAT initiation, during-NAT the total time of NAT treatment, during-FTY the total time of FTY therapy, and switching period the therapy-free interval between the last NAT infusion and commencement of FTY. Patients had received NAT and FTY for at least 12 months. Shown is the ARR for single patients (dots) and the mean. Statistical analysis was performed using the Wilcoxon signed-rank test. Tests of significance are given by the p value.

To identify predictors of relapses after cessation of NAT and subsequent FTY treatment, we performed a univariate regression analysis with clinically relevant variables. Only the last EDSS during the switching period was significantly differently distributed in patients with and without relapse during FTY (p = 0.04) and significantly predicted the occurrence of relapse activity during FTY (p = 0.04) (Table 2). By ROC an EDSS >3 obtained in the switching period was identified, separating between patients with and without relapse during FTY therapy with a sensitivity of 64% and specificity of 88% (area under the

Table 2. Identification of predictors of relapses during FTY therapy. Univariate logistic regression analysis with relapse during FTY (no=0, yes=1) as depended variable.

Variable	*p* value (univariate logistic regression)
ARR prior to NAT	0.62
ARR during NAT	0.12
ARR during switching period	0.33
EDSS at start of NAT	0.06
Last EDSS during NAT	0.08
Last EDSS during switching period	**0.04**

FTY: fingolimod; ARR: annual relapse rates; NAT: natalizumab; EDSS: Expanded Disability Status Scale.

Table 3. Clinical characteristics after EDSS stratification (shown are mean and standard deviation (SD) or median and interquartile range (IQR)).

	EDSS ≤3 (n = 20)	EDSS>3 (n = 11)	*p* value
Gender (female)	54.5% (12/20)	60% (6/11)	1.0[d]
Age at onset of NAT (years)	36.7 (SD 10.7)	34.5 (SD 10.2)	0.8[c]
Disease duration prior NAT (years)	6.9 (SD 6.4)	9.4 (SD 5.6)	0.1[c]
Duration of NAT therapy (months)	34.7 (SD 14.4)	33.5 (SD 16.4)	0.8[c]
Number of NAT infusions	32.8 (SD 13.8)	31.5 (SD 12)	0.6[c]
Therapy-free episode (weeks)	15.3 (SD 3.7)	14.7 (SD 5.3)	0.4[c]
Duration of FTY therapy (weeks)	81.35 (SD 16.27)	72.73 (SD 19.74)	0.14[c]
ARR prior to NAT[a]	2 (IQR 2) (n = 19)	2 (IQR 2.12) (n = 10)	0.8[c]
ARR during NAT	0 (IQR 0)	0 (IQR 0.9)	**0.04**[c]
ARR during switching period[b]	0 (IQR 0)	0 (IQR 2.5)	0.8[c]
ARR during FTY	0 (IQR 0)	0.9 (IQR 2.0)	**<0.001**[c]

NAT: natalizumab; ARR: annual relapse rates; FTY: fingolimod; EDSS: Expanded Disability Status Scale. [a]Last year prior to NAT. [b]Extrapolated to one year. [c]Mann-Whitney-Exact-Test. [d]Fisher's-Exact-Test.

curve (AUC) (95% confidence interval (CI)) 0.71 (0.52–0.91), p = 0.04). Both groups (EDSS ≤3 vs. EDSS >3) did not differ in patient characteristics with the exception of ARR during NAT being significantly higher in patients with EDSS >3 prior to FTY initiation (Table 3). In the patient population with EDSS >3, relapses during FTY occurred significantly more frequently (relapse during FTY: EDSS ≤3 5/20 (25%) vs. EDSS >3 9/11 (82%), p = 0.007) and the corresponding ARR was significantly higher than in patients with EDSS ≤3 (EDSS ≤3: mean ARR 0.24 (SD 0.69) vs. EDSS >3: mean ARR 1.35 (SD 1.25); p = 0.001) (Figure 2, Table 3). Comparing patients with EDSS >3 with those ≤3, the relative risk for a relapse during FTY was 3.27 (95% CI: 1.5–7.3). Neither the change of EDSS between the last measurements during NAT and in the switching period, nor disease duration at initiation of FTY had a significant influence on relapse activity during FTY (data not shown).

In a second step all patients with relapses during NAT were excluded from analysis to focus on NAT responders and to eliminate the influence of ARR during NAT, which was distributed differently in patients with EDSS ≤3 vs. >3 (Table 3) and also showed a tendency toward a different distribution in patients with and without relapse during FTY (p = 0.05). Still our finding remained significant, demonstrating a favorable response to FTY also in NAT responders with less severe disability (n = 23; EDSS ≤3: mean ARR 0.19 (SD 0.66), EDSS >3: mean ARR 1.12 (SD 1.05); p = 0.003, relative risk for a relapse during FTY: 4.27 (95% CI 1.59–14.01).

Discussion

Finding a safe and still efficacious therapy after NAT discontinuation is an unsolved problem of great clinical relevance for patients with active RRMS. Because disease-modifying drugs like IFN and GLAT have

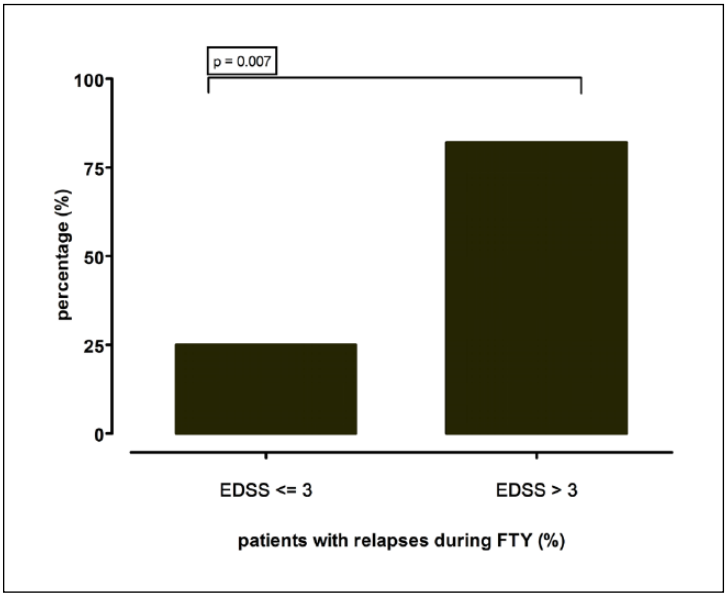

Figure 2. Occurrence of any relapse during FTY therapy in patients stratified for EDSS.
EDSS was measured after NAT discontinuation and before start of FTY. EDSS ≤3 *n* = 20, EDSS >3 *n* = 11. Fisher's-Exact-Test was used for statistical analysis.
FTY: fingolimod; EDSS: Expanded Disability Status Scale; NAT: natalizumab.

revealed limited efficacy, FTY is often used as subsequent therapy, even though previous studies have shown that at least 50% of patients who switch from NAT to FTY experience relapses after NAT discontinuation.[6] It is therefore of interest to identify features that might help to predict the risk of relapses after switching from NAT to FTY.

We describe that EDSS >3 after withdrawal of NAT is a predictor for relapses during subsequent FTY therapy. Seventy-five percent of patients with EDSS ≤3 remained free of relapses, compared to only 18% of patients with EDSS >3. Interestingly, EDSS >3 was also a predictor of subsequent relapses in the subgroup who had been relapse free during NAT therapy. We additionally observed that patients with relapses during NAT therapy also tend to have relapses during FTY, although this finding was not statistically significant. In order to reduce confounding effects, we excluded patients with relapse activity during NAT. Yet, EDSS >3 remained a significant predictor. We also evaluated whether or not EDSS was differently distributed between patients with and without relapse during NAT or correlated with relapse frequency during NAT and thus might be a general relapse predisposing factor. Here our analysis demonstrated no significant influences (data not shown).

The EDSS 3 milestone as predictor of relapses after cessation of NAT has not been described before and is clinically relevant for treating physicians. One obvious explanation could be that a higher EDSS reflects higher clinical disease activity during NAT and previous therapies as demonstrated by a significantly higher ARR during NAT in patients with EDSS >3 in comparison to EDSS ≤3. However, ARR during NAT did not significantly influence relapse activity during FTY, and EDSS 3 remained a significant predictor of relapses during FTY even after excluding patients with relapses during NAT. Since both EDSS at start of NAT and the last EDSS during NAT also tended to be associated with relapse activity during FTY, clinical disability measured by EDSS per se seems to be an important predictor.

Another explanation for the EDSS 3 cut-off could be that even though all patients included in this observation were still in the relapsing–remitting phase, patients with an EDSS >3 are at considerable risk for transition to the secondary progressive phase.[14] The EDSS cut-off for onset of invariable clinical deterioration was confirmed by Scalfari et al., estimating a mean EDSS of 2.9 (SD 0.047) at onset of secondary progression.[15] This transition from the relapsing to the progressive disease course often is associated with reduced efficacy of immunomodulatory drugs and might also explain reduced effectiveness of FTY in our cohort. It has to be mentioned that subgroup analysis of the FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis

(FREEDOMS) trial did not report differences in the ARR or disability progression between FTY-treated patients with an EDSS <3.5 vs. >3.5.[16] However, patients did not have an NAT withdrawal prior to FTY and the predefined EDSS cut-off of 3.0 was post-hoc changed to 3.5.

It is current clinical practice and still advisable to initiate FTY treatment in patients who want to stop NAT, mainly because FTY was shown to reduce the recurrence of disease activity, contrary to "drug holidays" or switching to first-line therapies.[6] In analogy to the described EDSS >3 cut-off after NAT withdrawal, it might also be considered in patients with higher physical disability during NAT therapy, characterized by EDSS >3, to continue NAT after risk-benefit assessment (particularly in JCV antibody-negative cases) or to change to emerging options such as alemtuzumab or B-cell depleting therapies. Hitherto safety and efficacy of the latter post-NAT switching strategies are unknown. In contrast, in patients with low-grade disability (EDSS ≤3) switching from NAT to FTY seems to be safe and effective, and therefore in our opinion may be recommended if no contraindications for FTY therapy exist.

Limitations of our investigation include the low sample number, the retrospective design and the lack of comprehensive MRI data. As a consequence, prospective observational studies with a larger sample size should be performed to verify our retrospective results by multivariate regression analysis.

In conclusion, our data indicate that RRMS patients switching from NAT to FTY are at considerable risk for relapses during the first six months after NAT withdrawal. Stratification by EDSS might help physicians to individualize risk calculation. Further studies are needed to improve the individual risk-benefit assessment prior to NAT withdrawal and decision whether to switch to FTY or alternative therapies.

Conflicts of Interest

Dr Hoepner has received travel expenses and research grants from Biogen-Idec and travel expenses and personal compensation from Novartis.
Dr Havla has received speaker honoraria, travel expenses and personal compensations from Merck-Serono, Novartis Pharma and Biogen-Idec.
Dr Eienbroeker has nothing to declare.
Dr Tackenberg has received travel reimbursements, speaker and consulting honoraria from Bayer Healthcare, Biogen Idec, Genzyme, Merck Serono, Novartis Pharma, Sanofi-Aventis and Teva Pharma as well as research support from Bayer Healthcare, Biogen-Idec and Novartis Pharma.
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Dr Hohlfeld is supported by the Deutsche Forschungsgemeinschaft and the KKNMS and has received personal compensations from Bayer Healthcare, Teva Pharma, Merck-Serono, Biogen-Idec, Novartis Pharma, Sanofi-Aventis and Genzyme.
Dr Gold has received speakers and consulting honoraria, and scientific grant support from Bayer Healthcare, Biogen-Idec, Merck-Serono, Novartis Pharma and Teva Pharma.
Dr Kümpfel has received travel expenses and personal compensations from Bayer Healthcare, Teva Pharma, Merck-Serono, Novartis Pharma, Sanofi-Aventis and Biogen-Idec as well as grant support from Bayer-Schering AG and Novartis Pharma.
Dr Kleiter reports receiving travel expenses and personal compensations from Bayer Healthcare, Biogen-Idec, Chugai, Merck Serono and Novartis as well as research support from Bayer Healthcare, Novartis Pharma and Biogen-Idec.

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