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What to expect after natalizumab cessation in a real-life setting

Salhofer-Polanyi S, Baumgartner A, Kraus J, Maida E, Schmied M, Leutmezer F, the Austrian Tysabri Registry Group. What to expect after natalizumab cessation in a real-life setting.
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Background – To minimize the risk of progressive multifocal leucoencephalopathy (PML), treatment with natalizumab is often stopped after 2 years, but evidence upon rebound of disease activity is limited and controversial. *Objective* – To evaluate effects of natalizumab discontinuation on clinical disease activity within twelve months after cessation. *Methods* – We retrospectively analyzed data of 201 patients with MS who discontinued natalizumab between 2007 and 2012. Mean change scores of annualized relapse rate (ARR) and expanded disability status scale (EDSS) were calculated for detection of rebound disease activity after twelve months. *Results* – Natalizumab exposure did not exceed 2 years in 50.2% of patients, and the most common reasons for discontinuation were a long treatment period and concern of PML (56%). A total of 11.9% experienced a rebound phenomenon within twelve months. Mean ARR prenatalizumab was lower ($P = 0.001$, 95% CI −1.0–0.000) and treatment response to natalizumab poorer ($P < 0.001$, 95% CI 0.4–1.3) in patients with rebound compared to those without, but rebound was not associated with brief exposure to natalizumab ($P = 0.159$, 95% CI −9.3–1.5). 86.1% of patients switched to another therapy. Patients without rebound were found more often in the group starting an alternative treatment early ($P = 0.013$). *Conclusion* – Our data suggest that rebound of MS disease activity affects a subgroup of patients (11.9%), especially those with low disease activity before natalizumab therapy and a longer treatment gap after its withdrawal.

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Introduction

Since its approval as monotherapy for the treatment of highly active relapsing–remitting multiple sclerosis (MS), natalizumab represents a highly effective considerable treatment option for MS patients with poor response to first-line immunomodulatory drugs, or an aggressive disease course from onset (1–3). In addition to its clinical effects, natalizumab also proved to significantly reduce disease activity on MRI (2, 4). However, long-term treatment is associated with sustained alteration of circulating peripheral immune cells (5) and seems to be associated with activation of JC virus and the occurrence of progressive multifocal leucoencephalopathy (PML) with the peak of PML risk after 2 years of treatment (6, 7). Driven by the fear of PML, both patients and physicians often decide to interrupt natalizumab treatment, regardless of its treatment effectiveness. Some experts do support this approach, which aims to allow reorganization of the immune system, thus theoretically preventing PML. However, several reports raise concerns about a rebound phenomenon (defined as worsening of disease activity beyond pretreatment levels) (8–12) or at least a quick return of disease activity to pretreatment levels in patients with highly active MS (13, 14). Recently, a large post hoc analysis of data from the AFFIRM, SENTINEL, and GLANCE studies, all formal registration studies, did not show evidence of a rebound effect (13). Nevertheless, these data refer to patients with MS, recruited prior to first PML

cases, when treatment with natalizumab was not yet restricted to certain groups of patients with an unfavorable disease progression. Overall, evidence on a rebound effect of MS disease activity following natalizumab discontinuation remains controversial.

The objective of this study was to evaluate effects of natalizumab treatment discontinuation on clinical and MRI disease activity levels in a real-life setting.

Patients and methods

Approved by the local ethics committee, this study used the Austrian TYSABRI registry to retrospectively select data of patients, aged between 18 and 65 years, who discontinued natalizumab treatment between October 2007 and December 2012.

The Austrian TYSABRI registry, developed by the Austrian Society of Neurology, was introduced in 2006 for safety reasons and is part of a pharmacovigilance program, further determining the requirements of specialized MS centers. Enrollment of both patients and treating physicians in the registry is mandatory, ensuring close clinical follow-ups every 3 months. Since 2008, costs of natalizumab treatment are only covered by the public healthcare system, provided that patients are recorded in this registry. Information on MS disease activity and natalizumab treatment was obtained from the TYSABRI registry. To obtain more detailed information for this study, treating physicians were asked to complete and return a questionnaire, covering questions both on clinical and MRI disease activity after natalizumab discontinuation.

A total of 984 patients were recorded in the registry and 374 of them had discontinued natalizumab treatment. A final number of 201 complete questionnaires were returned by 20 specialized MS centers located all across Austria and determined the scale used for this study. Rebound of disease activity was defined as clinical worsening beyond pretreatment levels and was measured by mean change scores of ARR and EDSS. MRI data were also collected, and progression on MRI was defined as an increase in gadolinium-enhancing lesions and T2 lesion load. Further demographic characteristics and baseline values are given in Table 1.

Table 1 Clinical characteristics of patients prenatalizumab ($n = 211$)

Gender, % female	78.1
Mean age (start natalizumab), years (SD)	34.9 (9.7)
Mean age, years (diagnosis MS)	25.7 (8.4)
Mean disease duration (start natalizumab), years (SD)	9 (0.08–30.7)
Median EDSS score prior to natalizumab	3.0
ARR prior to natalizumab (SD)	2.2 (1.1)
MS therapy within 1 year prior to natalizumab, % patients	
Glatiramer acetate	34.3
Interferon beta 1a	25.4
Intravenous immunoglobulins	12.4
No therapy	9.0
Several therapy attempts	7.4
Interferon beta 1b	6.0
Mitoxantron	2.5
Cyclophosphamide	1.0
Teriflunomide	1.0
Plasmapheresis	0.5
Fingolimod	0.5

SD, standard deviation; MS, multiple sclerosis; EDSS, Expanded Disability Status Scale.

Statistical analysis

Descriptive statistics (mean, ± standard deviation, median, or frequencies and percentages) are given for all variables. Calculation of mean change scores of ARR and Expanded Disability Status Scale (EDSS) (12-month follow-up minus prenatalizumab), was carried out in order to show if, and to what extent, a subgroup of patients experienced a rebound of disease activity. Thus, a negative value implies improvement and a positive value worsening. The data of patients experiencing an increase in disease activity were compared with the respective results of the stable disease course group. For comparison between different observation points and groups, parametric or nonparametric tests were used. Chi-square test or Fisher's exact test were used for proportions. Analysis was performed using SPSS 20. All P-values <0.05 were considered statistically significant.

Results

Mean time of natalizumab treatment prior to treatment discontinuation was 24.5 ± 12.7 months. Natalizumab exposure did not exceed 12 months, 24 months, and 36 months in 22.7%, 27.6%, and 33.6% of patients, respectively. Only 16.1% of patients received natalizumab for more than 36 months. The three most common reasons given for not continuing natalizumab treatment were: a long treatment period (24.4%), JCV seropositivity (12%), and fear of PML (10.5%). In addition, following reasons (among others) were recorded: high disease activity during natalizumab treatment (9.6%), combination of a long treatment period and JCV seropositivity (9.1%), desire for children (5.7%), pregnancy (4.3%),

persistent antibodies against natalizumab (2.4%), upon patient's request (3.8%), allergy (3.8%), and residence abroad (2.4%). Of 15.6% of patients who recorded side effects, only 1.4% therefore stopped treatment.

MS disease activity as measured by ARR improved statistically significant during natalizumab treatment compared with pretreatment levels ($P < 0.001$, 95% CI 1.5–1.8), and, without reaching pretreatment levels, increased again after discontinuation of natalizumab ($P < 0.001$, 95% CI 1–1.5): mean ARR prenatalizumab, during natalizumab, and twelve months after natalizumab discontinuation was 2.2 (±1.1), 0.5 (±0.9), and 1.1 (±1.3), respectively ($P < 0.001$). Median EDSS score decreased from 3.0 prenatalizumab to 2.5 ($P < 0.001$, 95% CI 0.000–0.25) at the time of natalizumab withdrawal, and, compared with pretreatment levels, was 3.0 after twelve months ($P = 0.702$, 95% CI 0.000–0.25). A total of 60.9% of patients experienced a relapse within 1 year after natalizumab discontinuation.

Mean change score of ARR (twelve months follow-up minus prenatalizumab) was -1.1 ± 1.5. Negative values indicating a relapse rate lower than pretreatment level were found in 88.1% of patients and positive values indicating worsening beyond pretreatment levels ('rebound') in 11.9% of patients. A statistically significant difference in clinical characteristics between these two groups was found regarding prenatalizumab ARR and response to natalizumab treatment (defined as ARR on natalizumab minus prenatalizumab): mean ARR prenatalizumab was lower ($P < 0.001$, 95% CI −1.0–0.000) and treatment response poorer ($P < 0.001$, 95% CI 0.4–1.3) in the rebound group. Mean ARR in the rebound and no-rebound group was 1.5 and 2.3 prenatalizumab, 0.7 and 0.5 while on natalizumab, and 3.3 and 0.8 twelve months after natalizumab discontinuation, respectively. Comparison of ARR (95% CI 2.0–3.0) and ARR mean change scores (95% CI 3) in patients with and without rebound showed a statistically significant deterioration at twelve months in the rebound group ($P < 0.001$). Comparison of EDSS mean change scores showed a statistically significant deterioration at 12 months in the rebound group ($P = 0.015$, 95% CI 0.000–1.5). Occurrence of rebound was not associated with exposure time to natalizumab ($P = 0.159$, 95% CI −9.3–1.5). Table 2 shows a detailed compilation of these results and characteristics of the two groups.

The majority of patients (86.1%) switched to an alternative MS treatment after natalizumab discontinuation, the most common being fingolimod (33.3%) and glatiramer acetate (13.5%), 7.2% restarted natalizumab, and 4.4% tried more than one treatment. The proportion of patients not undergoing further treatment within the observation period was almost the same in the rebound (12.5%) and no-rebound (13.7%) groups ($P = 0.871$). Alternative treatment was started within 3, 6, 9, and 12 months after discontinuation of natalizumab in 56.9%, 26.0%, 3.9%, and 1% of patients. Start of alternative treatment early within 3 months after natalizumab discontinuation was found more often in patients without rebound ($P = 0.013$). There was no association between duration until initiation of alternative treatment and disease activity prior to natalizumab therapy ($P = 0.503$), thus excluding a potential bias that patients with more active disease prior to natalizumab might have received earlier alternative treatment. Results are summarized in Table 3 and Fig. 1 shows treatment strategies in the rebound and no-rebound groups after natalizumab discontinuation.

MRI data were available in a subgroup of patients, and results are summarized in Table 4. Pretreatment MRI showed no statistically significant differences between the rebound and no-rebound groups regarding T2 lesion load and presence of more than one gadolinium-enhancing lesion. Within 1 year after natalizumab discontinuation, more patients in the rebound group developed gadolinium-enhancing lesions and

Table 2 Characteristics of patients with and without rebound 12 months after discontinuation of natalizumab

Parameter (SD)	No rebound $n = 177$	Rebound $n = 24$	*P*-value
Gender, % female	77.4	79.1	0.914[a]
Mean age, (start natalizumab) years	34.8 (9.9)	35.1 (7.7)	0.866[b]
Mean age, (diagnosis MS), years	26 (9)	25 (7)	0.910[c]
Mean disease duration, years	9 (6.3)	9.6 (5.1)	0.656[b]
Mean natalizumab exposure, months	25.3 (12.7)	21.4 (12.2)	0.159[b]
Mean ARR prenatalizumab	2.3 (1.1)	1.5 (0.9)	0.001[c]
Mean ARR on natalizumab	0.5 (0.9)	0.7 (1.0)	0.730[c]
Mean ARR 12 months post-natalizumab	0.8 (0.9)	3.3 (1.8)	<0.001[c]
Median EDSS prenatalizumab	3.0	3.5	0.816[c]
Median EDSS on natalizumab	2.5	2.5	0.770[c]
Median EDSS 12 months post-natalizumab	2.5	4.0	0.148[c]
Relapse free on natalizumab, % patients	55.9	58.3	0.870[a]
Relapse free 12 months post-natalizumab, % patients	44.6	0	<0.001[a]

SD, standard deviation; ARR, annualized relapse rate.
[a]Fisher's exact test.
[b]*t*-test.
[c]Mann–Whitney *U*-test.

Table 3 Alternative treatment after natalizumab discontinuation in patients with and without rebound

Parameter	No rebound (n = 177), %	Rebound (n = 24), %	P-value[a]
Time to alternative treatment 0–3 months			
0–3 months	60.6	37.5	0.013
>3 months	25.7	50	
No alternative treatment	13.7	12.5	0.871
Same treatment prior to and after natalizumab therapy	12.5	0	0.072
Subgroup analysis			
Fingolimod	35.4	20.8	0.156
0–3 months[b]	23.4	8.3	
>3 months[b]	12	12.5	
Glatiramer acetate[b]	14.3	12.5	
0–3 months	13.1	12.5	
>3 months	1.2	0	
Interferon beta 1a[b]	6.8	4.1	
0–3 months	3.4	4.1	
>3 months	3.4	0	

[a]Chi-square test.
[b]Chi-square test was not carried out due to limited sample size in these subgroups.

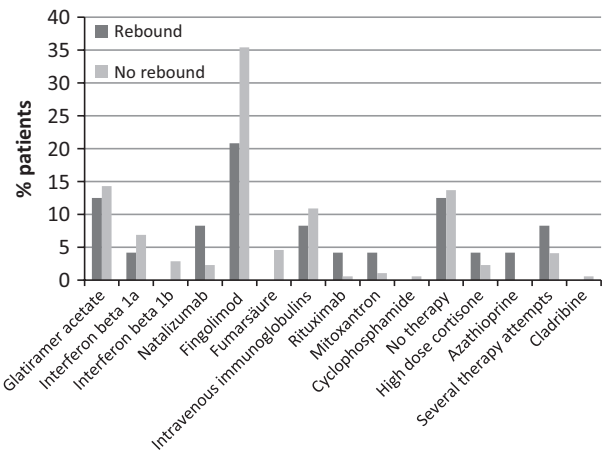

Figure 1. Treatment following natalizumab discontinuation.

progression on MRI scan ($P < 0.001$). The majority of patients both in the rebound (60.9%) and no-rebound (48.9%) groups had an MRI scan 4–6 months after natalizumab discontinuation.

Discussion

We analyzed data of more than 200 patients, who discontinued natalizumab for a variety of reasons. The key finding was that a subgroup of patients with MS (11.9%) experienced a rebound of disease activity. Up to now, restart of clinical and MRI disease activity some months after natalizumab discontinuation, and return to pretreatment levels, was observed in all relevant studies (8, 10, 11, 13), but evidence of a rebound phenomenon remained controversial, especially because patients with partly disastrous rebound of disease activity were reported in several case reports and small patient series (8, 10–12, 15). The percentage of patients with clinical disease activity and prenatalizumab treatment characteristics in our cohort is similar, compared with these studies. The most likely explanation for lower relapse frequencies in two studies was the inclusion of patients with secondary or primary progressive multiple sclerosis (10, 11). However, direct comparison between these studies is flawed by different rebound definitions. We defined rebound as worsening of disease activity beyond pretreatment levels as measured by ARR and EDSS, while other studies were based on the development of new and/or enlarging T2 lesions (9), relapse severity and number of gadolinium-enhancing lesions (10), relapse severity with sustained EDSS worsening (8), or ARR and gadolinium-enhancing lesions (13). An important question remaining after all studies is which subgroup of patients is at risk of experiencing a rebound of disease activity. Brief exposure (range of 1–8 infusions) to natalizumab leading to partial immunosuppression with sudden influx of viable activated lymphocytes after discontinuation was suggested to be a risk factor for MRI and clinical rebound (9, 16). However, we could not find an association between rebound risk and both duration of exposure and younger age, as reported previously in another study (16). Most strikingly, mean ARR prenatalizumab in our patients with rebound was lower and treatment response to natalizumab poorer (although it was still good) compared to those without rebound. We cannot offer an explanation for these

Table 4 Summary of available MRI data in patients with and without rebound

Parameter	No rebound, %	Rebound, %	P-value[a]
>9 T2 lesions prenatalizumab	n = 61	n = 10	0.99
Yes	96.7	100	
No	3.3	0	
>1 Gd-enhancing lesion prenatalizumab	n = 165	n = 22	1.0
Yes	63.6	63.6	
No	36.4	36.4	
MRI progression post-natalizumab	n = 136	n = 23	<0.001
Yes	25.0	69.6	
No	75	30.4	
Gd-enhancing lesions post-natalizumab	n = 130	n = 23	<0.001
Yes	23.8	65.2	
No	76.9	34.8	

[a]Chi-square test.

observations and comparison with other studies is not valid, as none had detailed within-group comparisons (rebound vs no rebound) of their results. While other studies agreed on a more prominent disease activity return in patients with higher disease activity prenatalizumab, our results, to the contrary, suggest that patients with higher ARR prenatalizumab are at lower risk to develop a rebound phenomenon. Yet, pathophysiological correlates of disease activity return to pretreatment levels and beyond pretreatment levels may not be the same, and the phenomenon of 'regression to the mean' may also contribute to this finding. The clinical significance of this finding is not clear, and it certainly deserves further research if patients with higher disease activity prior to natalizumab are indeed at lower risk to develop rebound after discontinuation and which other factors contribute to the risk of rebound. Recently, a small pilot study showed that clinical and radiological disease activity following natalizumab discontinuation was closely linked to natalizumab saturation on T cells, thus representing a possible tool to monitor rebound risk (17).

Recently published data strongly recommends reinstatement of alternative treatment following discontinuation of natalizumab to reduce the risk of rebound (10–12). Yet, no alternative treatment proved to sufficiently control MS disease activity following natalizumab discontinuation. The percentage of patients in this study, who switched to other DMTs, was similar in both the rebound and no-rebound group. However, a statistically significant difference was found regarding the time from natalizumab discontinuation to the start of alternate therapies. We therefore propose that alternate therapy should be started early, ideally within 3 months after cessation of natalizumab. In any case, alternative treatment should be initiated before the peak of return of disease activity after natalizumab discontinuation is expected, which is around 3–6 months. Recently, one group proposed to start glatiramer acetate during the last 3 months of natalizumab therapy (8), and according to another open-label pilot study, glatiramer acetate is effective in controlling MS disease activity following discontinuation of natalizumab when established within 4 weeks after natalizumab was stopped (18). To delay therapy based on and attracted by data showing a sustained natalizumab effect with stable disease course of at least 6 months (19) cannot be recommended, at least to our point of view.

However, our finding of a rebound phenomenon is contradictory to another retrospective analysis, failing to find rebound activity in a large cohort of patients from the AFFIRM, SENTINEL, and GLANCE studies of natalizumab (13). This difference may be due to study settings. Our results were derived from real-life settings and patients with an unfavorable disease course to whom prescription of natalizumab is restricted, whereas the latter study relied on formal registration trials, when the association of natalizumab and PML was still unknown. Stüve et al. and Kaufmann et al. also could not find a rebound of disease activity in their cohort of patients, but both studies share the limitation of sample sizes being quite small (19, 20).

Our study has several limitations. First, analysis of data was carried out retrospectively. Second, MRI scans were carried out on a routine basis and not for trial purpose. Therefore, MRI protocols were poorly standardized. Third, complete questionnaires were not available from all patients recorded in the registry. Nonetheless, our results were derived from patients in real-life settings, thus representative for the population of patients with MS, receiving natalizumab in daily routine practice.

Our data analysis clearly demonstrates that rebound of MS disease activity following natalizumab discontinuation has to be expected in a subgroup of patients, especially those with a relatively small disease activity before initiation of natalizumab treatment. Early reinstatement of alternative treatment within 3 months after natalizumab discontinuation might help to prevent this rebound effect. Further research is necessary to better identify characteristics of patients, who are at risk of developing a rebound of disease activity.

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Conflict of interest

On behalf of all authors, the corresponding author declares that there is no conflict of interest, disclosures, or financial relationships deemed relevant to the manuscript.

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Appendix 1

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