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Clinical trial

Long-term disease activity and disability progression in relapsing-remitting multiple sclerosis patients on natalizumab

I. Dekker[a,b,*], C.E. Leurs[b], M.H.J. Hagens[b], Z.L.E. van Kempen[b], I. Kleerekooper[b], B.I. Lissenberg-Witte[c], F. Barkhof[a,d], B.M.J. Uitdehaag[b], L.J. Balk[b], M.P. Wattjes[a,e], J. Killestein[b]

[a] Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Radiology & Nuclear Medicine, MS Center Amsterdam, Amsterdam Neuroscience, De Boelelaan 1117 Amsterdam, the Netherlands
[b] Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Neurology, MS Center Amsterdam, Amsterdam Neuroscience, De Boelelaan 1117 Amsterdam, the Netherlands
[c] Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Epidemiology and Biostatistics, Amsterdam Neuroscience, De Boelelaan 1117 Amsterdam, the Netherlands
[d] Institutes of Neurology and Healthcare Engineering, UCL, London, United Kingdom
[e] Department of Diagnostic and Interventional Neuroradiology, Hannover Medical School, Hannover, Germany

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ABSTRACT

Background: Natalizumab is an effective treatment for relapsing-remitting multiple sclerosis (RRMS). Data on clinical and imaging measures predictive of disease activity and progression during treatment is limited.

Objective: To determine clinical and imaging predictors of long-term inflammatory disease activity and disability progression in RRMS patients on natalizumab.

Methods: Patients (*n* = 135) were selected from our prospective observational natalizumab cohort and monitored using brain MRI and extensive clinical testing. Progression and improvement on the Expanded Disability Status Scale (EDSS), no evidence of disease activity (NEDA) and no evidence of progression or active disease (NEPAD) status were determined using measurements after the initial phase of inflammation and the early anti-inflammatory impact of natalizumab.

Results: EDSS progression was seen in 43.7% of patients and EDSS improvement in 17.8%. Median follow-up was 4.9 years (IQR 3.6–6.0). Patients with a longer disease duration at natalizumab initiation have a higher hazard for earlier EDSS progression (HR 1.05, CI 1.00–1.09, *p* = 0.037) and a higher pre-baseline relapse rate predicted a longer NEPAD status (HR 1.70, CI 1.06–2.72, *p* = 0.028).

Conclusion: The results suggest that starting natalizumab early, during active inflammatory disease results in a more favourable outcome. When taking into account early inflammation and the impact of natalizumab on disease activity during the initial treatment phase, a higher than expected proportion of patients showed disability progression.

1. Introduction

Relapsing-remitting multiple sclerosis (RRMS) is an inflammatory, demyelinating disease, mostly starting in young adults (Compston and Coles, 2008). Various immunomodulatory and immunosuppressive treatments are effective in terms of lowering inflammatory disease activity and improving clinical outcome. It is, however, still difficult to predict which individual RRMS patient will benefit from a particular treatment and to what extent (Killestein et al., 2011). Natalizumab (Tysabri, Biogen Inc, Cambridge, MA, USA), a humanised monoclonal antibody constraining the migration of leukocytes over the blood–brain barrier (Rudick and Sandrock, 2004), is a well-established effective treatment in RRMS (Polman et al., 2006). Numerous studies showed a decrease in the annualised relapse rate (ARR) and stabilisation (Polman et al., 2006; Butzkueven et al., 2014; Pucci et al., 2011; Johnson et al., 2015; Havrdova et al., 2009) or even improvement (Phillips et al., 2011; Prosperini et al., 2017; Laroni et al., 2014; Prosperini et al., 2015) of physical disability, measured by the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). Also, a reduction in the number of new T2-hyperintense lesions and T1-gadolinium enhanced lesions is consistently reported (Pucci et al., 2011; Prosperini et al., 2016; Zivadinov et al., 2016). These clinical and

imaging outcome measures comprise the goal of therapy; to achieve a status of 'No Evidence of Disease Activity' (NEDA) or 'No Evidence of Progression or Active Disease' (NEPAD) (Havrdova et al., 2010). Although natalizumab has shown to be an effective therapy in RRMS patients, little is known about parameters predicting the outcome. Some post-marketing studies have focussed on the prediction of a favourable outcome after natalizumab initiation; EDSS improvement (Kallweit et al., 2012; Sargento-Freitas et al., 2013) or maintaining NEDA (Prosperini et al., 2016; Prosperini et al., 2012). Most of these studies had a short follow-up (FU) with only one long-term FU study (Prosperini et al., 2016). These studies yielded different but inconclusive predictors, moreover, imaging predictors were barely investigated. Identifying predictors for treatment efficacy is of clinical relevance to recognize the patients who will benefit most from natalizumab. Disability improvement could be a result of the initial, expected reduction in active inflammation effectuated by natalizumab (Kappos et al., 2013). Exclusion of this initial period of active inflammation to measure disability changes, gives better insight into the long-term effects of natalizumab on disability. Therefore, the aim of this study was to determine clinical and imaging predictors for long-term disease activity and disability changes, including NEDA and NEPAD status, in a large, prospective cohort of natalizumab treated RRMS patients excluding the first period of active inflammation.

2. Methods

2.1. Patient selection

Patients were selected from an ongoing prospective observational cohort study, which was initiated in 2006 at the VU University Medical Center Amsterdam. Patients were included in this natalizumab cohort study if they were 18 years or older at start of the natalizumab treatment. Patients were monitored at yearly intervals, using brain MRI and clinical testing. For the present study, only patients with at least two follow-up assessments, including a complete visit one year after baseline were included. Patients selected for more thorough subanalyses, calculating NEDA and NEPAD as an outcome measure, required complete year 1 MRI data and at least two complete radiological and clinical FU moments.

Prior to study inclusion, written informed consent was obtained from all participants. The local institutional review board issued a waiver stating that the requirements of the Medical Research Involving Human Subjects Act did not apply for the use of the clinical and imaging data for this study.

2.2. MRI data acquisition

MRI protocols included proton-density (PD)/T2-weighted and post-contrast T1-weighted images. Slice thickness was 3 mm with an in-plane resolution of 1mm^2. Brain MRI scans were performed on a 1.5 Tesla or a 3.0 Tesla scanner in the VU University Medical Center Amsterdam. Image acquisition differed among patients (i.e. magnetic field strengths, pulse sequences, head coils and spatial resolution), which was taken into consideration by the raters in the radiological analyses. Nonetheless the MRI acquisition followed the recently published Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) expert panel guidelines (Wattjes et al., 2015; Rovira et al., 2015).

MRI scans were obtained at baseline and yearly for John Cunningham (JC) virus negative patients, and 3-monthly for patients with a JC virus antibody positive status, according to the progressive multifocal leukoencephalopathy (PML) pharmacovigilance protocol (Traboulsee et al., 2016; Kappos et al., 2011; McGuigan et al., 2016). For this study the yearly scans were checked for new disease activity. Spinal cord MRIs were not included in the analyses for NEDA and NEPAD.

2.3. Endpoints and assessments

2.3.1. EDSS progression or improvement

Disability progression was defined as used in clinical trials with an increase in EDSS of 1.5, 1 or 0.5 in case of a reference EDSS of 0, 1–5 or ≥ 5.5 respectively (Uitdehaag, 2018). Disability improvement was defined as a decrease in EDSS of 1 or 0.5 in case of a reference EDSS of 1–5 or ≥ 5.5 respectively (Uitdehaag, 2018). To evaluate the course of disability, FU EDSS scores were compared. Importantly, we used the EDSS scores after 1 year of natalizumab treatment as the reference, in order to prevent bias by suboptimal treating effects within the first period of treatment and to exclude the impact of relapse recovery shortly after baseline in patients showing improvement (Kappos et al., 2013).

2.3.2. No evidence of disease activity (NEDA)

NEDA status (i.e. no clinical or radiological disease activity or confirmed EDSS progression) was determined during follow-up (Havrdova et al., 2010). Disability progression measured by EDSS was defined as mentioned above. In case of NEDA determination, we asserted a confirmation period of at least 6 months. By definition of EDSS progression, patients needed at least two FU moments to be able to confirm EDSS progression. A new relapse was defined as new neurological symptoms observed by a neurologist, lasting more than 24 h and not attributable to other causes than MS. Radiological activity was defined as a new or enlarged (> 50% increase in lesion size) lesion on T2-weighted images or a new gadolinium enhanced lesion. Baseline T1-gadolinium enhanced lesions and T1-hypointense lesions were categorised according to the presence of lesions or not. Baseline T2-hyperintense brain lesions were categorised as a low lesion number (0–30 lesions) or high number of lesions (>30 lesions). Lesions were counted by two raters (IK and MW).

To avoid capturing disease activity while natalizumab treatment was still suboptimal (Kappos et al., 2013), NEDA was calculated with the EDSS and MRI at the first available option after baseline, which was at 1 year follow-up and used this EDSS and MRI as the reference for the detection of changes at FU. Relapse information was used excluding the relapses occurring in the first 3 months of natalizumab treatment. The time maintaining NEDA was calculated and the reason of not maintaining NEDA was noted (new relapse > 3 months after natalizumab initiation, confirmed disability progression on EDSS after the first year, radiological disease activity after the first year on MRI scan).

2.3.3. No evidence of progression or active disease (NEPAD)

In addition to the definition of NEDA as described above, for NEPAD also the timed 25-foot walk test (25-FWT) and 9-hole peg test (9-HPT) are included to detect progression. A minimum of 20% worsening on the 25-FWT or the 9-HPT, confirmed after at least 6 months, was used as the threshold for the detection of disability progression. Disability progression for NEPAD was defined as progression on one of the three assessments (EDSS, 25-FWT, 9-HPT) (Wolinsky et al., 2018). Progression on EDSS, 25-FWT, 9-HPT or MRI during the first year of treatment was excluded. For relapse information the first 3 months of treatment were excluded. The time maintaining NEPAD and the reason of not maintaining NEPAD were described.

2.4. Statistical analysis

Descriptive statistics were used to describe baseline characteristics and outcome measures for the analysed groups. Kaplan Meier curves were used to calculate the time to the first event for the different outcome measures (EDSS progression and improvement, NEDA, NEPAD). Patients without an event were censored at their last moment of FU. The total number of patients with an event (EDSS progression, maintaining NEDA and maintaining NEPAD) is not corrected for censored patients. Cox-regression analysis with a forward selection procedure

and a cut-off value of 0.10 was used to identify baseline clinical and radiological predictors for the outcome measures. The proportionality assumption of the Cox regression model was investigated with the Schoenfeld residuals. The potential clinical predictors that were analysed were disease duration (defined as time difference between first symptoms and start of natalizumab treatment), sex, age and EDSS at baseline and the mean annual relapse rate over the 2 years prior to natalizumab treatment. The potential imaging predictors were the presence of baseline T1-gadolinium enhanced lesions and T1-hypointense brain lesions, and a low (0–30) or high (>30) number of T2-hyperintense brain lesions. Significance level for between group comparisons was set at 0.05. Analyses were performed using IBM SPSS statistics 22.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Disability progression and improvement

In total 135 patients of the initial cohort of natalizumab treated RRMS patients were included in this study. The median FU period was 4.9 years (IQR 3.6–6.0).

Patient demographics, clinical information and MRI characteristics are summarised in Table 1. In short, the mean age at baseline was 36.6 years (± 8.7), 67.4% of the patients was female, median baseline EDSS was 3.5 (IQR 2.5–5.1) and median disease duration 7.6 years (IQR 4.2–11.8). A large majority of patients (96.3%) used another DMT prior to natalizumab initiation (see Table 1).

Five of the excluded patients without at least 2 FU moments, stopped natalizumab treatment because of clinical progression. The other excluded patients did not reach the 2 FU moments yet or stopped before the second FU visit for other reasons, but not because of

Table 1
Patient characteristics.

	All patients
No. of patients (%)	135 (100%)
Age at natalizumab initiation, years (mean, SD)	36.6 (8.7)
Disease duration at BL, years (median, IQR)	7.6 (4.2–11.8)
Female sex (%)	91 (67.4)
EDSS at BL (median, IQR)	3.5 (2.5–5.1)
FU length, years (median, IQR)	4.9 (3.6–6.0)
ARR 2 years pre-natalizumab treatment (mean, SD)	1.24 (0.70)
Number of prior DMTs (median, IQR)	1 (1–2)
0 (no. of patients (%))	5 (3.7)
1 (no. of patients (%))	85 (63.0)
2 (no. of patients (%))	37 (27.4)
≥3 (no. of patients (%))	8 (5.9)
Type of DMT prior to natalizumab (no. of patients (%))	
No DMT	5 (3.7)
Only first line DMTs	115 (85.2)
Only second line DMT	1 (0.7)
Miscellaneous experimental DMT	4 (3.0)
Both first and second line DMT	7 (5.2)
First and miscellaneous experimental DMT	3 (2.2)
Baseline MRI data	
T1-Gd enhanced brain lesions	
No. of pts without (%)	35 (32.7)
No. of pts with (%)	72 (67.3)
T1-hypointense brain lesions	
No. of pts without (%)	32 (26.9)
No. of pts with (%)	87 (73.1)
T2-hyperintense brain lesions	
No. of pts with a low lesion number (0–30 lesions) (%)	47 (37.9)
No. of pts with high lesion number (>30 lesions) (%)	77 (62.1)

Table 1 shows the patient characteristics of all patients. First line therapies were mostly different types of interferons and glatiramer acetate. Second line therapy was mostly mitoxantrone.
ARR: annualised relapse rate, BL: baseline, DMT: disease modifying treatment, Gd: gadolinium, IQR: interquartile range, pts: patients, SD: standard deviation.

progression.

After the initial year of natalizumab treatment, 59/135 patients (43.7%) showed EDSS progression and 24/135 patients (17.8%) showed EDSS improvement.

3.2. No evidence of disease activity (NEDA)

Complete data on NEDA status was available for 84 patients and more than half of these patients (49/84, 58.3%) maintained NEDA irrespective of their FU time. Of the 35 patients (41.7%) who did not maintain NEDA, 16 patients (45.7%) showed confirmed EDSS progression, 12 patients (34.3%) encountered a relapse at least 3 months after natalizumab initation and 7 patients (20.0%) showed new disease activity on MRI compared to the MRI after 1 year of treatment.

3.3. No evidence of progression or active disease (NEPAD)

For NEPAD subgroup analysis, 65 patients were included. In total 23 patients (35.4%) maintained NEPAD irrespective of their FU time. Out of the 42 patients (64.6%) not maintaining NEPAD, the majority (76.2%) encountered disability progression (on EDSS, 25-FWT and/or 9-HPT), whereas others showed MRI-activity (7.1%) or had a relapse (16.7%).

3.4. Predicting disease activity and disability progression/improvement

The cumulative incidence of EDSS progression during natalizumab treatment is shown in Fig. 1a. The time to EDSS progression was predicted by a longer disease duration at natalizumab initation (HR 1.05, CI 1.00–1.09, $p = 0.037$) (Table 2). The cumulative incidence of EDSS improvement is shown in Fig. 1b, no predictors were identified for the time to EDSS improvement.

The probability of maintaining NEDA is shown in Fig. 1c. Cox-regression analyses did not reveal any of the potential clinical and radiological relevant characteristics to predict the time to disease activity or EDSS progression (losing NEDA). Fig. 1d shows the probability of maintaining NEPAD.

Cox-regression analyses revealed a higher annualised relapse rate over the two years before start of natalizumab to result in a lower hazard for a shorter time to an event for NEPAD (HR 0.59, CI 0.37–0.95, $p = 0.028$). In other words, a higher ARR gives a higher hazard for maintaining NEPAD status over a longer period (HR 1.70, CI 1.06–2.72, $p = 0.028$). This is visualised in Fig. 2 that shows the time-to-event for NEPAD for different values of the ARR.

The prediction models for the different outcome measures are summarised in Table 2.

In order to verify comparability between our study and other studies we also analysed the EDSS changes using the *baseline* EDSS instead of the year one measurement as a reference (Table 3). The proportionality assumption was valid for all covariates.

4. Discussion

This long-term follow-up study of natalizumab treated patients shows that a longer disease duration at natalizumab initiation predicts earlier EDSS progression and that patients with a higher pre-baseline relapse rate have a higher hazard to lose their NEPAD-status later. An important difference to previously published studies is the exclusion of the active inflammatory period to measure disability changes. This avoids capturing the expected disability improvement due to the anti-inflammatory effect of natalizumab during the initial active inflammation. Moreover, while the anti-inflammatory effects of natalizumab could be suboptimal in the beginning of treatment, this is omitted by excluding the first year of natalizumab treatment for disability progression and new lesions, and excluding the first three months for relapses (Kappos et al., 2013).
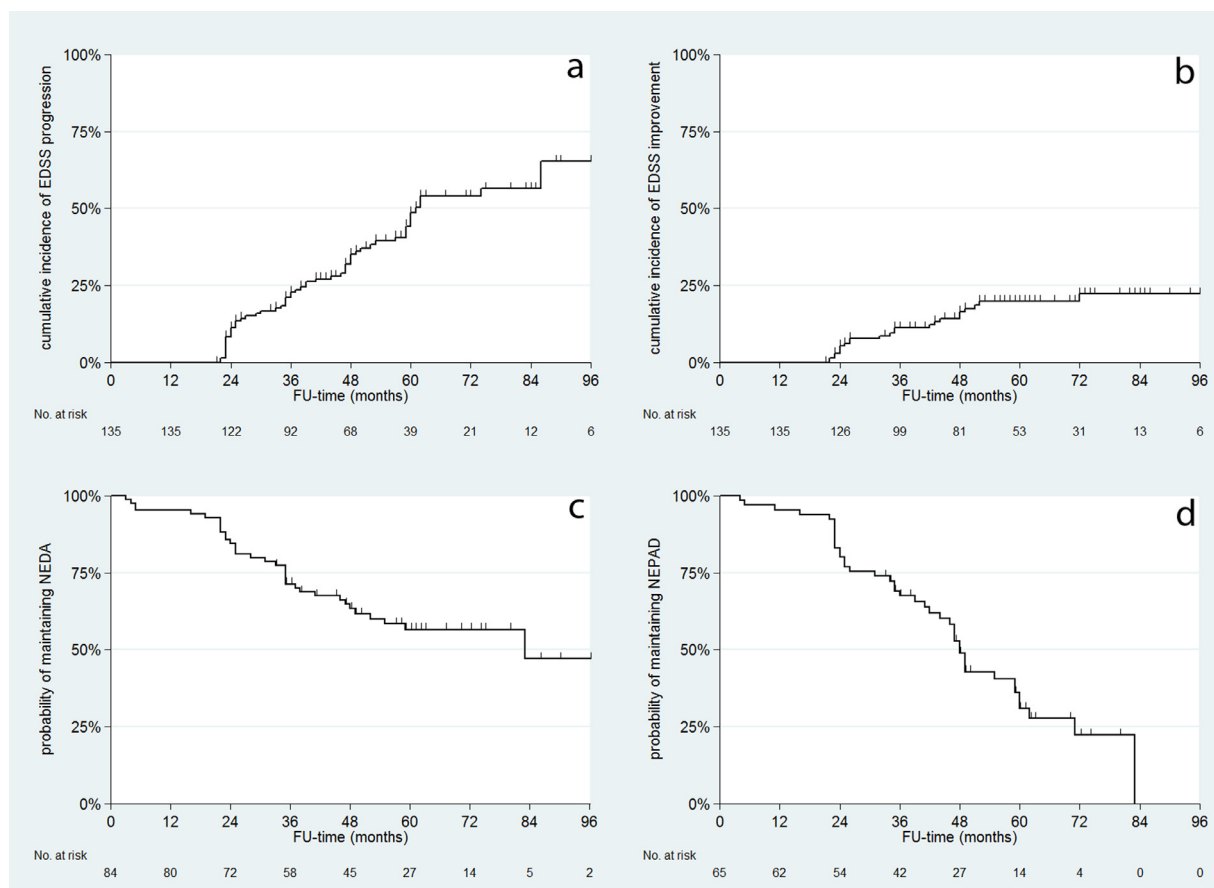
Fig. 1. Cumulative incidence of EDSS progression (a) and EDSS improvement (b) and the probability of maintaining NEDA (c) and NEPAD (d) in months, during natalizumab treatment. This figure shows the number of patients at risk during FU and takes the time to event into account which causes a difference with the percentages mentioned in the text (the percentage of patients having an event during FU).
EDSS: Expanded Disability Status Scale, FU: follow-up, NEDA: no evidence of disease activity, NEPAD: no evidence of progression or disease activity.

Table 2
Prediction models.

Prediction models	HR	95% CI	*p*-value
EDSS progression			
Disease duration at BL (years)	1.05	1.00–1.09	0.037
NEPAD			
Pre-baseline ARR	1.70	1.06–2.72	0.028

Table 2 shows the prediction models for the time to EDSS progression and the time maintaining NEPAD. No predictors were identified for the time to EDSS improvement and the time maintaining NEDA. Predictors taken into account were: disease duration at baseline, sex, age at baseline, EDSS at baseline, pre-baseline annualised relapse rate, T1-gadolinium enhancing brain lesions, T1-hypointense brain lesions, T2-hyperintense brain lesions.
ARR: annualised relapse rate, BL: baseline, CI: 95% confidence interval; EDSS: Expanded Disability Status Scale, HR: hazards ratio.

The effectiveness of natalizumab has been proven in trials comparing natalizumab to placebo (Polman et al., 2006; Havrdova et al., 2009) and in studies comparing natalizumab to other MS therapies (Johnson et al., 2015; Prosperini et al., 2017; Rudick et al., 2006). Besides EDSS progression and improvement, NEDA status is increasingly used as an outcome measure. The majority (58.3%) of the patients in our study maintained NEDA during FU, which is in line with other studies (Havrdova et al., 2009; Prosperini et al., 2016; Prosperini et al., 2012; Belachew et al., 2011). The number of patients maintaining a status of NEPAD is markedly lower. NEPAD is a comprehensive outcome measure and is more sensitive in the detection of disability progression than the NEDA status. To our knowledge, no other study
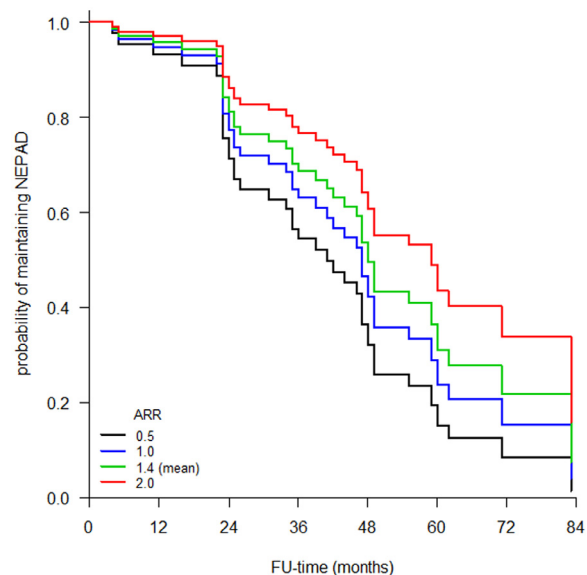

Fig. 2. Time-to-event for different values of the annualised relapse rate.
ARR: annualised relapse rate; FU-time: follow-up time; NEPAD: no evidence of progression or active disease.

determined and predicted NEPAD status for natalizumab treated patients yet, but the outcome measure is used in other trials, e.g. those testing efficacy of ocrelizumab (Wolinsky et al., 2018).

Table 3
EDSS development.

Baseline EDSS as reference	Frequency	Percentage
EDSS progression (confirmed)	45	34.6% (16.2%)
Stable	35	26.9%
EDSS improvement (confirmed)	50	38.5% (18.5%)
Total	130	

Year 1 EDSS as reference	Frequency	Percentage
EDSS progression (confirmed)	59	43.7% (15.6%)
Stable	52	38.5%
EDSS improvement (confirmed)	24	17.8% (5.9%)
Total	135	

Table 3 shows the number and percentage of patients having EDSS progression or improvement. The number between brackets represents the at least 6 months confirmed EDSS progression or improvent. The upper part of the table shows the EDSS progression or improvement referred to the baseline EDSS and the lower part of the table shows the EDSS progression and improvement with the year 1 EDSS as a reference as displayed throughout the manuscript. This table provides insight into the impact of using different EDSS measurements as a reference.

EDSS: Expanded Disability Status Scale.

Predictors for disability progression, disability improvement and disease activity during natalizumab treatment have been poorly established. Different and in particular clinical predictors have been considered, but did not reveal unambiguous predictors for disability progression, disability improvement or disease activity during natalizumab treatment. Most studies conducted in daily clinical settings were limited by small sample sizes and focussed on disability improvement or 'optimal treatment response' for which different definitions were used (Laroni et al., 2014; Prosperini et al., 2016; Sargento-Freitas et al., 2013; Belachew et al., 2011).

Our study suggests that a high pre-baseline ARR is a predictor for maintaining NEPAD over a longer time. None of the potential clinical or imaging baseline parameters was predictive for NEDA in our study, although one could expect a similar outcome for NEDA and NEPAD, this could have been due to the different number of patients but most likely, the 25-FWT and 9-HPT increased the number of patients with disability progression. Moreover, the percentage of patients encountering MRI-activity or relapses was lower for NEPAD than for NEDA, possibly because disability progression was earlier present than relapses or new lesions. However, this could also possibly explain why a high ARR was a predictor for longer NEPAD-status as slow ongoing progression is probably not so strongly inhibited by natalizumab as inflammation. In agreement to our findings, suggesting that a high pre-baseline ARR predicts longer NEPAD-status, a high pre-baseline ARR as a predictor for an optimal response has been suggested in other studies as well (Laroni et al., 2014; Sargento-Freitas et al., 2013; Belachew et al., 2011; Kalincik et al., 2017). The largest of these studies is a recent, extensive 'real world' observational multi-centre study suggesting that natalizumab treated patients with a high pre-baseline ARR have a higher chance of regression of disease (Kalincik et al., 2017). Also conflicting results have been published. Data from a study including 152 patients on natalizumab suggested that patients with a lower ARR and a lower baseline EDSS have a higher chance of maintaining NEDA during FU (Prosperini et al., 2016). In addition, a 2-year follow-up study suggested that lower pre-natalizumab ARR and low baseline EDSS were predictors for NEDA (Prosperini et al., 2012). A comparison between these studies is difficult as various different definitions were used for an optimal response and none of the studies used NEPAD as an outcome measure. Besides the pre-baseline ARR, former studies suggested also a lower EDSS, lower age and shorter disease duration at baseline (Sargento-Freitas et al., 2013) as well as an EDSS between 3.0 and 3.5 (Laroni et al., 2014) as predictors. Compared to our study, these studies had smaller patient numbers (ranging from 48 to 62 patients) and

shorter FU. From our results we hypothesize that patients with a more active disease at baseline have more effect of natalizumab in terms of NEPAD which could be due to a more inflammatory component of their disease or could suggest that patients with a lower ARR are already in a more progressive, possibly predominantly neurodegenerative, disease course and therefore show earlier disability progression.

Predictors for EDSS progression in natalizumab treated patients have not been studied widely. Results of our study suggest that patients with a longer disease duration at the start of natalizumab indicates earlier EDSS progression during FU. Patients with a longer disease duration could have less effect of natalizumab when the inflammatory disease component slows down and a more neurodegenerative process dominates. However, not many patients ($n = 5$) stopped treatment because of disease progression. The focus of most studies has been on disability improvement, but due to the low number of patients achieving EDSS improvement, our study could have been underpowered to detect EDSS improvement. Although, the most likely explanation of a lower proportion of patients showing improvement during natalizumab is the fact that we used the year one measurement as reference, excluding patients showing improvement due to a reduction of disease activity immediately after natalizumab initiation and regression to the mean.

Thus, the key difference between our study and previously published studies is the exclusion of the first year of treatment when analysing disease progression. To allow better comparisons with previous reports by others, we also analysed the EDSS progression and improvement using the baseline EDSS as a reference (Table 3). These calculations show comparable percentages of confirmed EDSS progression but lower percentages for confirmed EDSS improvement than the pivotal trials and subsequent studies on these patients (Polman et al., 2006; Butzkueven et al., 2014; Havrdova et al., 2009; Phillips et al., 2011).

The number of patients showing EDSS progression is higher using year 1 as a reference. The difference in EDSS improvement using year 1 as a reference instead of baseline is even more remarkable (Table 3). EDSS improvement during the first year could be due to a very active disease at natalizumab initiation because that has been a main reason to select natalizumab as a treatment. Patients could still have a delayed relapse recovery after a period with a high relapse rate which was also suggested by a small study in natalizumab patients showing that 41% of the patients with EDSS improvement had a sustained EDSS worsening in the year prior to natalizumab initiation (Belachew et al., 2011). Using unconfirmed EDSS progression could lead to an overestimation of improvement or progression but since EDSS was not obtained during or within 3 months from a relapse, this could have had minor influence only.

Notably, imaging predictors have been studied less than clinical predictors (Prosperini et al., 2015; Rudick et al., 2006) and so far, imaging predictors were not consistently found (Phillips et al., 2011). This, together with the fact we did not identify relevant imaging predictors, corresponds with the advice that the pre-treatment MRI should not be used to predict therapy outcome (Wattjes et al., 2015).

Large longitudinal cohorts are necessary to identify the patients who will benefit most from therapy. Important to note is that reaching a disease free status is not the only goal because the individual patient could also benefit from lower disease activity by reduction of the inflammation. The low number of studies conducted on predictors of disease activity, disability progression, disability improvement, NEDA and NEPAD so far, and the differences in study design make comparisons challenging. Other interesting imaging features that could not be included in the present study, but could be of interest for future studies are brain atrophy and spinal cord involvement (both lesions and atrophy).

In conclusion, in this longitudinal cohort study of natalizumab treated patients, a higher than expected proportion of patients showed disability progression, taken into account the impact of initial

improvement shortly after the start of natalizumab treatment. Long disease duration before the start of natalizumab predicted earlier EDSS progression. A high pre-baseline ARR predicted a lower chance of losing NEPAD-status early. These results suggest that starting treatment in an early phase of the disease in patients with high (inflammatory) disease activity may result in a more favourable outcome.

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