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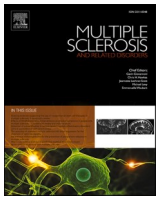

Original article

Natalizumab treatment of multiple sclerosis — a Danish nationwide study with 13 years of follow-up

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ABSTRACT

Background: Natalizumab is a widely used high-efficacy treatment in multiple sclerosis (MS). Real-world evidence regarding long-term effectiveness and safety is warranted. We performed a nationwide study evaluating prescription patterns, effectiveness, and adverse events.

Methods: A nationwide cohort study using the Danish MS Registry. Patients initiating natalizumab between June 2006 and April 2020 were included. Patient characteristics, annualized relapse rates (ARRs), confirmed Expanded Disability Status Scale (EDSS) score worsening, MRI activity (new/enlarging T2- or gadolinium-enhancing lesions), and reported adverse events were evaluated. Further, prescription patterns and outcomes across different time periods ("epochs") were analysed.

Results: In total, 2424 patients were enrolled, with a median follow-up time of 2.7 years (interquartile range (IQR) 1.2–5.1). In recent epochs, patients were younger, had lower EDSS scores, had fewer pre-treatment relapses and were more often treatment naïve. At 13 years of follow-up, 36% had a confirmed EDSS worsening. On-treatment ARR was 0.30, corresponding to a 72% reduction from pre-initiation. MRI activity was rare, 6.8% had activity within 2–14 months from treatment start, 3.4% within 14–26 months, and 2.7% within 26–38 months. Approximately 14% of patients reported adverse events, with cephalalgia constituting the majority. During the study, 62.3% discontinued treatment. Of these, the main cause (41%) was due to JCV antibodies, while discontinuations due to disease activity (9%) or adverse events (9%) were less frequent.

Conclusion: Natalizumab is increasingly used earlier in the disease course. Most patients treated with natalizumab are clinically stable with few adverse events. JCV antibodies constitute the main cause for discontinuation.

1. Introduction

Natalizumab is a humanized, monoclonal antibody binding to the α_4-subunit of integrin proteins on immune cells, preventing migration of immune cells across the blood-brain-barrier (Polman et al., 2006). The pivotal trials (AFFIRM, SENTINEL) demonstrated beneficial effects of natalizumab in relapsing-remitting MS on relapse-occurrence, worsening of disability and new T2 or gadolinium-enhancing lesions on MRI (Polman et al., 2006; Rudick et al., 2006). In the pivotal trials natalizumab showed a generally advantageous safety profile, but was temporarily withdrawn from the market following development of PML in two patients in the extension phase of the SENTINEL trial (Kleinschmidt-DeMasters and Tyler, 2005; Langer-Gould et al., 2005). Although uncommon, this potentially lethal adverse event has introduced risk stratification schemes using JCV antibodies, which are measured before and during therapy (Sørensen et al., 2012).

Until January 2008, treatment with natalizumab was limited to two centers In Denmark, and from 2006 to March 2011 natalizumab

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treatment required two or more relapses or sustained increase of 2 EDSS points on DMT in the previous year, or as de novo therapy very active MS (Oturai et al., 2009).

Today, natalizumab is recommended as treatment in the high-efficacy treatment tier in JCV-antibody negative patients. High-efficacy treatment is generally indicated in patients with high disease activity at diagnosis, or for patients with disease breakthrough on other DMTs (Danish Medicines Council, 2021).

While RCTs are gold-standard in establishing the clinical efficacy and safety of therapies, they might not reflect the clinical use of the treatment with regards to prescription patterns, demography, follow-up, adherence and reporting of adverse events. Some observational studies have explored the longer-term effectiveness of natalizumab, generally showing robust effects on both clinical and radiological disease activity and similar safety profile as the RCTs (Bigaut et al., 2021; Butzkueven et al., 2020; Horakova et al., 2020).

Using Danish nationwide data, we performed a study investigating the clinical and radiological effectiveness in relapsing-remitting MS patients treated with natalizumab. Further, we describe patient characteristics, the duration of treatment, causes for discontinuation, and the occurrence of adverse events.

2. Materials and methods

2.1. Study population

The Danish healthcare system is publicly funded, and all Danish inhabitants have access to free and equal health services, including MS treatment. Treatment with DMTs is conducted at public clinics that are mandatorily reporting data to the Danish Multiple Sclerosis Registry, which capture data on treatment, along with clinical and paraclinical disease measurements. This information is entered by the treating neurologist at regular clinical visits, which are usually performed at treatment start, after 3 months and subsequently every 6 months. Data on anti-JCV- and anti-natalizumab antibody status are captured in the registry (Magyari et al., 2021). In Denmark, patients undergoing natalizumab treatment are tested for anti-JCV antibodies before starting and every 6 months. Patients tested JCV-positive during treatment are usually discontinued, however, patients with low-titer antibodies may continue treatment under increased MRI surveillance, if deemed advantageous. Anti-natalizumab antibodies are tested for at 3, 6, and 12 months after treatment start (Jensen et al., 2012). If a patient becomes persistently positive (confirmed 2 and 3 months after the initial positive test), treatment is discontinued. Adverse events are reported by patients and entered into the registry at clinical visits.

Individual-level linkage with other registries is possible using the Central Persons Registry (Schmidt et al., 2014), enriching the registry with demographics, vital status, and assessment of completeness (Koch-Henriksen et al., 2015).

In this study, we included all MS patients who initiated intravenous natalizumab between marketing launch in Denmark (June 2006) and the 1st of April 2020 (date of data extraction) with 4-weeks interval dosing. For patients who started natalizumab treatment on multiple occasions during this period, only the first treatment sequence was included. Baseline was defined as the date of natalizumab initiation. Patients were observed until the first occurrence of the following: termination of natalizumab treatment, emigration, death, or the date of data extraction. We defined a valid baseline EDSS as any valid score registered no longer than 8 months prior to baseline.

2.2. Efficacy outcomes

Relapses were recorded in the DMSR database by treating neurologists. A relapse is defined as an acute or subacute evolvement of a new symptom or a significant deterioration of a previously existing deficit lasting at least 24 h, and which was not due to infections or other non-neurologic disease. Relapses within 30 days from a previous relapse were considered as part of the same relapse.

Confirmed disability worsening (CDW) was defined as sustained increase in the EDSS score on two consecutive visits at least 24 weeks apart. Required thresholds of worsening were 1.5 points in patients with a baseline EDSS score of 0; 1 point in patients with a baseline EDSS score between 1 and 5.5; or 0.5 points in patients with a baseline EDSS above 5.5. We defined the outcome date as the date of the first EDSS worsening (and not the confirming date).

Likewise, confirmed disability improving (CDI) was defined as a decrease in the EDSS score of 1 point for patients with a baseline EDSS score between 1 and 5.5, or 0.5 points for patients with a baseline EDSS above 5.5, confirmed after 24 weeks. As above, the outcome date was defined as the date of first recorded EDSS improvement.

For MRI activity, we acquired data on the number of new or enlarging T2 lesions and appearances of gadolinium-enhancing lesions. MRI scans are usually performed are usually performed 3 to 6 months after treatment initiation and subsequently once every year. Gadolinium-enhancement is only administered at diagnosis, or if a severe relapse is suspected. If an entry contained any information on absence or presence of gadolinium-enhancing lesions, we assumed that the scan was performed with contrast. For the efficacy outcomes, we defined MRI activity as any occurrence of new or enlarging T2 lesions or presence of any gadolinium-enhancing lesions. For each patient, the first MRI scan performed after natalizumab initiation was excluded, as any activity recorded may have occurred while on previous/no treatment (re-baseline scanning). Subsequent MRI scans were included and allocated to three time periods: 2 to 14 months after natalizumab initiation, 14 to 26 months after natalizumab initiation, and 26 to 38 months after natalizumab initiation. The same patient could have included MRI scans in multiple time periods, according to the timing and availability of these. If multiple MRI scans for the same patient were available in the same time period, any MRI scan showing activity would define the patient as having activity in that period.

2.3. Treatment epochs

We stratified the study population in three time periods (hereafter "epochs") according to the year of first natalizumab initiation.

The epochs have been defined according to the availability of other disease modifying drugs of similar efficacy and thereby used for the same treatment indication.

- **2006–2011** – Patients initiating natalizumab between 1st of June 2006 and 31st of December 2011.
- **2012–2018** – Patients initiating natalizumab between 1st of January 2012 and 31st of December 2018.
- **2019–2020** – Patients initiating natalizumab between 1st of January 2019 and 1st of April 2020.

2.4. Statistical analysis

Statistical analyses were performed in SAS version 9.4 (SAS Institute Inc.).

We reported descriptive continuous variables using means and standard deviations (SD) or medians and interquartile ranges, as appropriate. Binary variables were described using counts and percentages.

Any differences in baseline demographic and clinical characteristics between treatment epochs were tested with a chi-squared test of independence for categorical variables and with a non-parametric Kruskal–Wallis test by ranks for continuous variables. If the overall test returned a significant result (p value < 0.05), a post-hoc analysis was performed to assess which epochs differed from each other and a correction for multiple comparisons was employed (Dunn's test with a Benjamini–Hochberg correction for Kruskal–Wallis test; Tukey-type

adjusted p-values based on 100 permutations for chi-squared test).

Time to reach first 24 weeks-CDW and first 24 weeks-CDI were investigated using the Kaplan-Meier method. For the time to reach 24 weeks-CDW and CDI analyses only patients with an available baseline EDSS score and at least 2 EDSS score during follow-up separated by a minimum of 6 months were included. For the time to reach first 24-weeks CDI, patients with a baseline EDSS score less than one were further excluded from the analysis.

A multivariable Cox regression model stratified by epochs was used to investigate the association of 24 weeks-CDW and 24 weeks-CDI with relevant baseline covariates (sex, age at natalizumab initiation, age at onset, EDSS score at baseline, relapses in the year prior natalizumab initiation, previous use of DMTs).

Annualized relapse rate (ARR) during natalizumab treatment and changes in ARR between 1-year pre-initiation and during the entire follow-up period were estimated using a negative binomial regression model together with cluster robust standard errors to account for overdispersion of the data and pairing of patients.

2.5. Ethics

This study was approved by the Danish Data Protection Agency (journal no. RH-2017-347, I-Suite no: 06058). Non-interventional register-based studies do not require ethical approval in Denmark.

2.6. Data availability

Anonymized data will be shared on request from any qualified investigator under approval from the Danish Data Protection Agency and the board of the DMSR.

3. Results

3.1. Baseline characteristics and treatment adherence

A total of 2424 patients were included in the study. Of these, 1774 patients were eligible for the analysis of EDSS worsening and 1715 were eligible for the analysis of EDSS improvement. Baseline characteristics are shown in Table 1.

When stratifying by epochs, a total of 961 patients initiated natalizumab from 2006 to 2011, 1252 from 2012 to 2018, and 211 from 2019 to 2020.

With advancing calendar year, we observed a decrease in the age at treatment start, a corresponding decrease in disease duration, a higher proportion of treatment naïve patients, a decreasing baseline relapse rate, and a lower baseline EDSS.

Descriptive data on treatment characteristics are shown in Table 2.

The median treatment duration was 2.7 years, with shorter follow-up durations with advancing epochs. At data extraction, 915 patients were currently continuing natalizumab treatment, while 1509 had discontinued. The most commonly specified reasons for natalizumab discontinuations were JCV antibodies (41%), pregnancy (11%), anti-natalizumab antibodies (9.3%; 5.8% of the total natalizumab-exposed population), disease activity (9%), and adverse events (9%).

3.2. Clinical efficacy outcomes

3.2.1. Time to 24-weeks confirmed disability worsening (CDW)

A total of 1774 patients with a valid baseline EDSS score and 2 subsequent EDSS scores were eligible for this analysis (116 excluded due to no baseline EDSS, and 534 without 2 post-baseline EDSS scores at least 24 weeks apart). Within these, 352 patients had 24-weeks CDW (19.8%), of which 277 events (78.8%) were sustained at the last available EDSS score (15.6% of patients). The average time elapsed between the CDW confirmation date and the last available EDSS for sustained events was 2.4 years (SD 2.5 years; median =1.7; IQR 0.4–4.0 years). At 5 and 13 years of follow-up, 24.5% and 36.0% had met the outcome. The cumulative risk is shown in Fig. 1.

When stratifying by epochs, the absolute risks were similar between the earliest epochs. Due to limited follow-up, however, estimation of long-term outcome in the most recent strata was not possible. Details in supplemental Fig. S1.

Results of the Cox-regression model showed an increased hazard of CDW in males, patients with lower age at onset, higher age at natalizumab initiation, and lower baseline EDSS. Details in Table 3.

Baseline characteristics of excluded and included patients for this analysis are shown in supplemental Table S1.

3.2.2. Time to 24-weeks confirmed disability improvement (CDI)

1715 patients with a valid baseline EDSS score ≥ 1 and 2 subsequent EDSS follow-up scores were eligible for analysis (116 excluded due to no baseline EDSS, 534 without 2 post-baseline EDSS scores at least 24 weeks apart, 59 with a baseline EDSS=0). A total of 589 events occurred. Among these, 421 (71.5%) were sustained at the last available EDSS score (24.5% of patients). At 5 and 13 years of follow-up, 40.0% and 47.7% had met the outcome. The cumulative risk is shown in Fig. 2.

When stratifying by epoch, we saw a tendency towards an increased proportion of patients with CDI in the intermediate epoch (2012–2018) compared with the earliest epoch (2006–2011). We had insufficient follow-up to make interpretations for the most recent epoch. The cumulative risk is shown in supplemental Fig. S2.

Results of the Cox-regression model showed increased hazard of CDI in females, higher age at onset, lower age at natalizumab initiation, treatment-naïve patients, and with higher baseline EDSS. Details are listed in Table 4.

Baseline characteristics of excluded and included patients for this analysis are shown in supplemental Table S2.

3.3. Annualized relapse rates

Overall, the annualized relapse rate in the 12-month prior natalizumab initiation was 1.11 (CI 1.07–1.15). Annualized relapse rate on natalizumab therapy was 0.3 (CI 0.28 – 0.32), corresponding to a reduction of ~72% ($p<0.0001$).

In the 2006–2011 epoch, during which high disease activity was required to receive natalizumab therapy, the annualized relapse rate in the 12-month period prior to natalizumab initiation was 1.28 (CI 1.21–1.35). Annualized relapse rate on natalizumab therapy was 0.46 (CI 0.42–0.5), corresponding to a reduction of ~64% ($p<0.0001$).

In the 2012–2018 epoch, the annualized relapse rate in the 12-month period prior to natalizumab initiation was 1.00 (CI 0.95–1.06). Annualized relapse rate on natalizumab therapy was 0.16 (CI 0.14 – 0.18), corresponding to a reduction of ~84% ($p<0.0001$).

In the 2019–2020 epoch, the annualized relapse rate in the 12-month prior natalizumab initiation was 0.97 (CI 0.85–1.09). Annualized relapse rate on natalizumab therapy was 0.09 (CI 0.05 – 0.17), corresponding to a reduction of ~91% ($p<0.0001$).

A total of 203 patients experienced a relapse within 6 months after stopping natalizumab (13.5% of patients stopping).

3.4. MRI efficacy outcomes

After exclusion of the first performed MRI after natalizumab initiation (intended as a “re-baseline” MRI), a total of 263 patients had at least 1 MRI within 2–14 months after treatment start. Among these, 18 (6.8%) showed signs of activity (any new/enlarging T2 lesions or any gadolinium-enhancing lesions). Among 848 patients with at least 1 MRI between 14 and 26 months after natalizumab initiation, 29 (3.4%) showed signs of activity. Lastly, among 802 patients with at least 1 MRI between 26 and 38 months after baseline, 22 (2.7%) had signs of activity on MRI.

Table 1
Clinical and demographic characteristics at baseline.

	Overall 2006–2020	*Epochs* 2006–2011	2012–2018	2019–2020	*P value*
Study Population (N)	2424	961 (39.6)	1252 (51.7)	211 (8.7)	
Sex					0.63
Male	701 (28.9)	282 (29.3)	364 (29.1)	55 (26.1)	
Female	1723 (71.1)	679 (70.7)	888 (70.9)	156 (73.9)	
Age at treatment initiation		A	AB	B	**0.009**
Mean ± SD	38.4 ± 10.0	39.0 ± 9.4	38.2 ± 10.3	36.8 ± 10.9	
Median	38.4	38.8	38.5	36.0	
Q1	30.7	32.2	30.3	28.8	
Q3	45.5	45.4	45.6	44.5	
Age at treatment initiation (categorical)		A	B	B	**0.007**
<=24	222 (9.2)	66 (6.9)	128 (10.2)	28 (13.3)	
25–34	693 (28.6)	265 (27.6)	358 (28.6)	70 (33.2)	
35–44	863 (35.6)	377 (39.2)	424 (33.9)	62 (29.4)	
45–54	521 (21.5)	207 (21.5)	274 (21.9)	40 (19.0)	
=> 55	125 (5.2)	46 (4.8)	68 (5.4)	11 (5.2)	
Disease duration (since onset)		A	B	C	**<0.0001**
Mean ± SD	8.2 ± 6.9	9.2 ± 6.4	7.8 ± 7.3	6.6 ± 6.5	
Median	6.6	8.0	5.6	4.3	
Q1	2.7	4.1	2.0	1.4	
Q3	12.2	12.9	11.8	10.0	
Previous DMTs usage		A	B	C	**<0.0001**
Naïve	315 (13.0)	47 (4.9)	211 (16.9)	57 (27.0)	
Pre-treated	2109 (87.0)	914 (95.1)	1041 (83.1)	154 (73.0)	
Number of previous unique DMTs †		A	A	B	**<0.0001**
Mean ± SD	1.4 ± 0.9	1.4 ± 0.8	1.4 ± 1.0	1.2 ± 1.2	
Median	1	1	1	1	
Q1	1	1	1	0	
Q3	2	2	2	2	
Number of previous unique DMTs (categorical) †		A	B	C	**<0.0001**
0	315 (13.0)	47 (4.9)	211 (16.9)	57 (27.0)	
1	1173 (48.4)	553 (57.5)	526 (42.0)	94 (44.5)	
2	667 (27.5)	274 (28.5)	360 (28.8)	33 (15.6)	
>2	269 (11.1)	87 (9.1)	155 (12.4)	27 (12.8)	
Last DMT prior natalizumab initiation					
None	315 (13.0)	47 (4.9)	211 (16.9)	57 (27.0)	
Interferon	1033 (42.6)	637 (66.3)	379 (30.3)	17 (8.1)	
Glatiramer acetate	358 (14.8)	190 (19.8)	147 (11.7)	21 (10.0)	
Dimethyl fumarate	153 (6.3)	0 (0)	120 (9.6)	33 (15.6)	
Teriflunomide	273 (11.3)	0 (0)	208 (16.6)	65 (30.8)	
Mitoxantrone	83 (3.4)	76 (7.9)	7 (0.6)	0 (0)	
Fingolimod	175 (7.2)	0 (0)	160 (12.8)	15 (7.1)	
Other ‡	34 (1.4)	11 (1.1)	20 (1.6)	3 (1.4)	
Number of relapses 1 year prior initiation		A	B	B	**<0.0001**
Mean ± SD	1.1 ± 1.1	1.3 ± 1.2	1.0 ± 1.0	1.0 ± 0.9	
Median	1	1	1	1	
Q1	0	0	0	0	
Q3	2	2	1	1	
Number of relapses 1 year prior initiation (categorical)		A	B	B	**<0.0001**
0	745 (30.7)	269 (28.0)	409 (32.7)	67 (31.8)	
1	974 (40.2)	340 (35.4)	535 (42.7)	99 (46.9)	
>1	705 (29.1)	352 (36.6)	308 (24.6)	45 (21.3)	
Number of relapses 2 years prior initiation		A	B	C	**<0.0001**
Mean ± SD	1.6 ± 1.3	2.0 ± 1.5	1.4 ± 1.1	1.2 ± 1.0	
Median	1	2	1	1	
Q1	1	1	1	1	
Q3	2	3	2	2	
Number of relapses 2 years prior initiation (categorical)		*A*	*B*	*B*	**<0.0001**
0	448 (18.5)	157 (16.3)	240 (19.2)	51 (24.2)	
1	832 (34.3)	239 (24.9)	500 (39.9)	93 (44.1)	
>1	1144 (47.2)	565 (58.8)	512 (40.9)	67 (31.8)	
EDSS score at treatment initiation §		*A*	*B*	*C*	**<0.0001**
Missing*	116	6	90	20	
Mean ± SD	3.3 ± 1.7	3.9 ± 1.7	2.9 ± 1.6	2.4 ± 1.6	
Median	3.0	4.0	2.5	2.5	
Q1	2.0	2.5	2.0	1.5	
Q3	4.0	5.0	3.5	3.0	
EDSS score at treatment initiation (categorical)§		*A*	*B*	*C*	**<0.0001**
Missing*	116 (4.8)	6 (0.6)	90 (7.2)	20 (9.5)	
<= 3	1267 (52.3)	358 (37.3)	758 (60.5)	151 (71.6)	
>3	1041 (42.9)	597 (62.1)	404 (32.3)	40 (19.0)	

DMT: disease-modifying therapy; SD: standard deviation.
† Multiple instance of the same DMT were considered as one instance.
‡ Includes: azathioprin, methotrexate, immunoglobulins, treosulfane, daclizumab.

§ Latest EDSS score in the 8 months prior natalizumab initiation.

Significant differences across epochs for reported variables are indicated with letters, representing the results of pairwise comparisons tests with a false discovery rate (FDR) correction ran after the overall test p-value (column "p-value") is significant. Epochs sharing the same letter are not statistically different from each other, whereas epochs not sharing the same letter are statistically different from each other.

Table 2
Treatment characteristics during follow-up.

	Overall 2006–2020	*Epochs* 2006–2011	2012–2018	2019–2020
Study Population	2424	961 (39.6)	1252 (51.7)	211 (8.7)
Natalizumab treatment duration (in years)				
Mean ± SD	3.6 ± 3.0	5.0 ± 3.6	3.0 ± 2.0	0.5 ± 0.4
median	2.7	4.3	2.5	0.4
Q1	1.2	2.0	1.4	0.2
Q3	5.1	7.9	4.4	0.8
Number of patients discontinuing natalizumab				
On treatment at data cut-off	915 (37.7)	162 (16.9)	569 (45.4)	184 (87.2)
Discontinued	1509 (62.3)	799 (83.1)	683 (54.6)	27 (12.8)
Switching to a different DMT	1279 (52.8)	687 (71.5)	570 (45.5)	22 (10.4)
Next DMT after natalizumab discontinuation¶, N (% of switchers)				
Fingolimod	683 (53.4)	456 (66.4)	225 (39.5)	<= 3
Ocrelizumab	174 (13.6)	40 (5.8)	123 (21.6)	11 (50)
Dimethyl fumarate	69 (5.4)	22 (3.2)	45 (7.9)	<= 3
Glatiramer acetate	66 (5.2)	27 (3.9)	36 (6.3)	<= 3
Alemtuzumab	53 (4.1)	18 (2.6)	35 (6.1)	0 (0)
Interferon	47 (3.7)	32 (4.7)	15 (2.6)	0 (0)
Cladribine	43 (3.4)	5 (0.7)	34 (6)	4 (18.2)
Mitoxantrone	41 (3.2)	41 (6)	0 (0)	0 (0)
Rituximab	32 (2.5)	13 (1.9)	19 (3.3)	0 (0)
Immunoglobulin	27 (2.1)	14 (2)	13 (2.3)	0 (0)
Teriflunomide	18 (1.4)	8 (1.2)	10 (1.8)	0 (0)
Other‡	26	11	15	0 (0)
Number of MRI scans during follow-up	7542	3709	3712	121
Gadolinium-enhancement (% of total)	1163 (15.4%)	448 (12.1%)	688 (18.5%)	27 (22.3%)
Reason for discontinuation†				
Missing	3 (0.2)	2 (0.3)	1 (0.1)	0 (0)
Other reason	252 (16.7)	151 (18.9)	90 (14.6)	1 (3.7)
Anti-natalizumab antibodies	140 (9.3)	78 (9.8)	55 (9.1)	7 (25.9)
Adverse events	135 (8.9)	49 (6.1)	78 (11.4)	8 (29.6)
Pregnancy	169 (11.2)	68 (8.5)	97 (14.2)	4 (14.8)
Stable condition	5 (0.3)	4 (0.5)	1 (0.1)	0 (0)
JC virus	613 (40.6)	328 (41.1)	280 (41.0)	5 (18.5)
Contra indication	8 (0.5)	5 (0.6)	3 (0.4)	0 (0)
Lack of patient compliance	6 (0.4)	1 (0.1)	4 (0.6)	1 (3.7)
Patient is terminated§	29 (1.9)	14 (1.8)	15 (2.2)	0 (0)
Progression	13 (0.9)	9 (1.1)	4 (0.6)	0 (0)
Disease activity	136 (9.0)	90 (11.3)	45 (6.6)	1 (3.7)

MRI: magnetic-resonance imaging; JC: John Cunningham; DMT: disease-modifying therapy.

¶ Next DMT can be initiated in a later epoch.

† Percentages are relative to the total number of patients discontinuing natalizumab ("discontinued" category).

‡ Includes: azathioprin, Hematopoietic Stem Cell Transplantation (HSCT), immunoglobulins, treosulfane, daclizumab, ofatumumab.

§ Includes emigration and death.

3.5. Adverse events

Overall, 486 adverse events (AEs) were recorded. For 2083 patients (85.9%) no AEs were reported during the natalizumab treatment period, for 245 (10.1%) patients one AE was reported, and for 96 (4.0%) patients multiple AEs were reported.

The most reported AE was cephalalgia (368 events), followed by "unspecified infusion-related complications" (42 events), respiratory tract-related (pneumonia, acute infections, pharyngitis, sinusitis, nasopharyngitis; 14 events) and urinary tract infections (12 events). Progressive multifocal leukoencephalopathy (PML) was recorded in ≤3 cases, and likewise ≤3 cases were reported for toxic liver disease, post-zoster neuralgia and influenza-like symptoms were reported. For details, see Table 5.

4. Discussion

Using a nationwide registry-based cohort of natalizumab-treated patients, we observed high clinical effectiveness with regards to prevention of disability accrual, MRI activity and relapse occurrence. Further, tolerability was high with a low proportion of patients experiencing adverse events. Lastly, discontinuations due to disease activity or adverse events were generally low.

Patients administered natalizumab were comparable to those included in the AFFIRM trial with regards to sex distribution. However, patients in our study tended to be slightly older, have longer disease duration at baseline, higher EDSS scores, lower pre-treatment relapse frequency, and were more often previously treated with another DMT (Polman et al., 2006). Our cohort was more comparable to previously published observational cohort studies of patients starting natalizumab (Bigaut et al., 2021; Butzkueven et al., 2020; Putzki et al., 2010).

A previous Danish study of all patients treated with natalizumab between 2006 and January 2008, comprising 234 very active patients with a median observation time of 11.3 months (range 3.0–21.5), showed a decrease in the annualized relapse rate from 2.53 to 0.68 (73% reduction) (Oturai et al., 2009). With advancing epochs, we saw a pattern of natalizumab being increasingly prescribed to patients with less disease activity and to younger patients with lower disability, along with a tendency for increased use among treatment-naïve patients. This is in line with a previous Danish study, which observed a general increase in the use of high-efficacy treatments as the first choice of therapy with advancing calendar year (Buron et al., 2020). These changes in the prescription pattern may reflect an increased focus on the potential benefits of high efficacy therapy in the early stages of disease — particularly in patients with high disease activity (Fernández, 2017; Ontaneda et al., 2019).

Overall, the clinical effectiveness of natalizumab administered in Denmark was high. The 2-year probability of CDW of approximately 13% was somewhat lower to what was reported in the AFFIRM trial of 17%, which may be due to differing follow-up and patient characteristics, but also a longer confirmation period in our study (Polman et al., 2006). The probability of confirmed EDSS worsening at 10–13 years of follow-up was comparable to that reported in other real-world cohorts (Bigaut et al., 2021; Butzkueven et al., 2020). Likewise, the occurrence of CDI was consistent with previous evidence (Butzkueven et al., 2020), however, it is worth noting that events of CDI may represent a return to a basal level of disability after a transient relapse-associated worsening. This is suggested by the sharp incline of the incidence curve immediately after treatment initiation — an event which is common following recent clinical disease activity. This may also explain the increased CDI events in the 2006–2011 epoch, which had higher relapse activity at baseline.

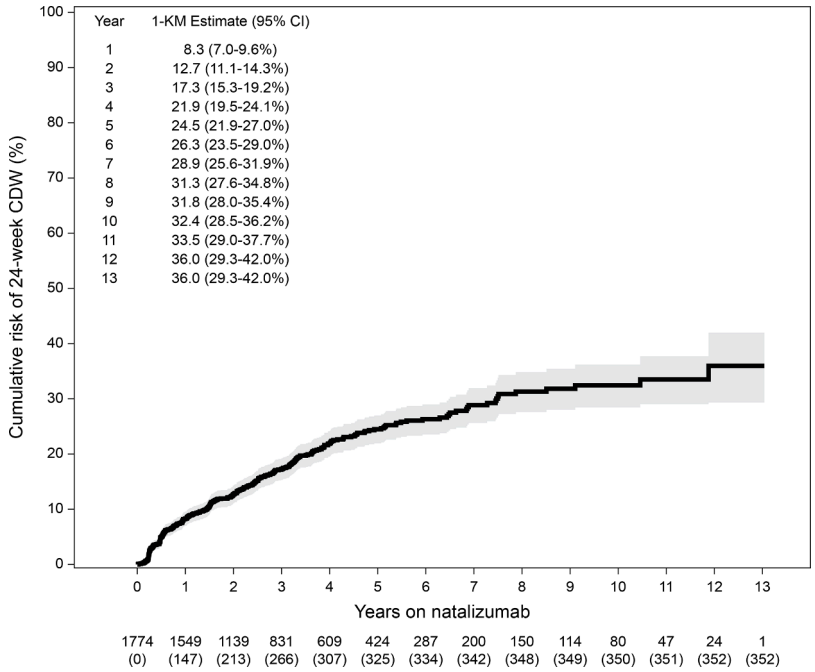

Fig. 1. Time to 24-weeks confirmed disability worsening (24-weeks CDW): Overall
Number of patients at risk and cumulative number of events (in parenthesis) are reported below the x axis. Time-point cumulative risks are reported in the top-left corner of the figure. CDW: confirmed disability worsening. 1-KM: inverse Kaplan–Meier. CI: confidence interval.

Table 3
24-weeks confirmed disability worsening, Cox-regression model.

Variable	*HR*	*Lower 95% CI*	*Upper 95% CI*	*P-value*
Sex				0.1986
Male (reference)	–	–	–	
Female	0.863	0.689	1.080	
Age at onset	0.975	0.959	0.991	**0.0022**
Age at Tysabri start	1.052	1.036	1.069	**<0.0001**
Previous DMT				0.5779
Naïve (reference)	–	–	–	
Pre-Treated	0.896	0.608	1.320	
EDSS score at baseline				**0.0242**
0 (reference)	–	–	–	
1 – 1.5	0.769	0.427	1.387	
2 – 2.5	0.561	0.323	0.974	
3 – 3.5	0.441	0.252	0.771	
4 – 4.5	0.428	0.239	0.767	
5 – 5.5	0.487	0.259	0.915	
6 – 6.5	0.525	0.293	0.940	
≥ 7	0.538	0.207	1.397	
Relapses 1 year prior				0.8340
0 (reference)	–	–	–	
1	0.942	0.730	1.215	
> 1	1.011	0.766	1.334	

CI: confidence interval, DMT: disease-modifying therapy, EDSS: Expanded Disability Status Scale.

Generally, patients with short follow-up durations were excluded from the EDSS outcomes, and this was more common in the latest epoch. Thus, significant differences reflected similar tendencies as those reported between early and later epochs (excluded patients were younger, had shorter disease durations, were more likely treatment naïve, had fever baseline relapses and lower EDSS scores). This may affect the generalizability of these analyses for these epochs.

The predictive factors for CDW consisted of lower age at disease onset and higher age at treatment start — a finding that is consistent with the previously observed higher risk of disability accrual in patients having a longer disease duration at treatment start (Bigaut et al., 2021; Dekker et al., 2019; Guger et al., 2021). We observed a decreased occurrence of CDW in patients with EDSS scores ≥3, which is contrary to previously reported protective effects of low baseline EDSS (Kalincik et al., 2017; Prosperini et al., 2016). Our results may be due to the EDSS being more dynamic in the lower parts of the scale (Wang et al., 2017).

The overall on-treatment annualized relapse rate was consistent with both previous RCTs and observational studies (Horakova et al., 2020; Polman et al., 2006). We saw a tendency for a reduction of on-treatment relapse occurrence with advancing epoch, which mainly could be explained by aforementioned shift in patient characteristics. Another explanation can relate to the study design, where patients undergo censoring upon treatment switching. With increased availability of alternative therapies in more recent epochs, MRI activity or other signs of insufficient disease suppression may prompt a change of therapy before a relapse occurs. When reporting reductions in ARR from pre-treatment to on-treatment periods, it is important to factor in the "regression to the mean"-effect. Usually, treatment initiations are performed following periods of transiently increased disease activity, and the activity level usually returns to a lower steady state afterwards. This effect often contributes to a higher perceived effect of the treatment (Martínez-Yélamos et al., 2006). Of those patients stopping natalizumab, 13.5% experienced any relapse within 6 months. It has previously been reported that 22% of Danish patients experienced rebound activity after cessation, as defined by an increase in ARR compared to pre-treatment levels. High on-treatment relapse activity was the main predictive factor for this (Sorensen et al., 2014).

Of those patients with valid MRI data, the majority showed no radiological activity (as defined by new or enlarging T2 lesions or gadolinium-enhanced lesions). The proportion of patients with radiological activity decreased with increasing time on treatment — a finding consistent with previous literature (Havrdova et al., 2009; Horakova et al., 2020). However, the proportion of patients having radiological disease activity in the first year after treatment start was lower in our cohort, compared with a Czech observational study (Horakova et al., 2020). A likely explanation for this could, however, be the "re-baselining" procedure performed in our study. A limitation of our study is the lack of standardised MRI protocols which likely reduce the quality of longitudinal assessments. MRI scans are performed routinely in

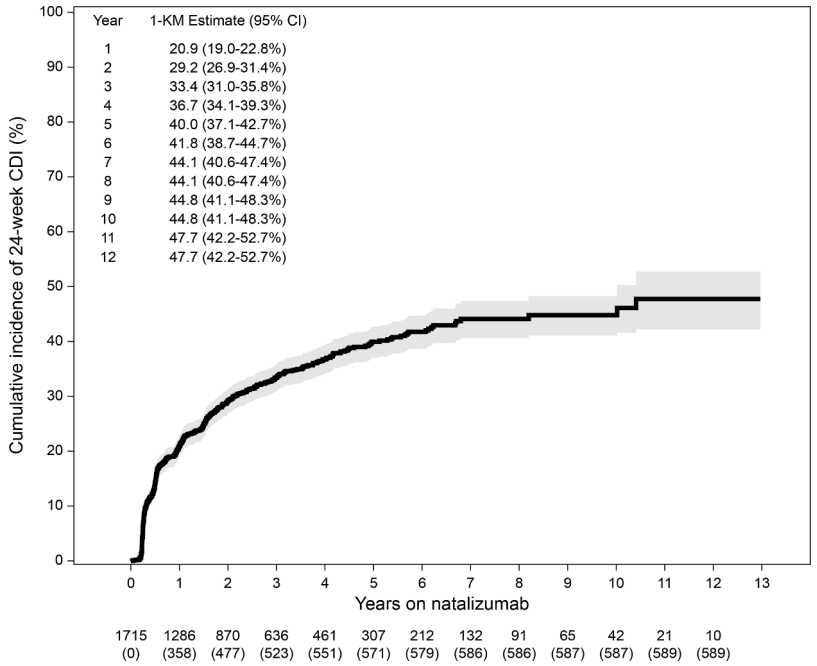

Fig. 2. Time to 24-weeks confirmed disability improving (24-weeks CDI): Overall
Number of patients at risk and cumulative number of events (in parenthesis) are reported below the x axis. Time-point cumulative risks are reported in the top-left corner of the figure. CDI: confirmed disability improvement. 1-KM: inverse Kaplan–Meier. CI: confidence interval.

Table 4
24-weeks confirmed disability improvement, Cox-regression model.

Variable	*HR*	*Lower CI*	*Upper CI*	*P-value*
Sex				**0.0187**
Male (reference)	–	–	–	
Female	1.243	1.037	1.491	
Age at onset	1.036	1.020	1.053	**<0.0001**
Age at Tysabri start	0.942	0.928	0.956	**<0.0001**
Previous DMT				**0.0051**
Naïve (reference)	–	–	–	
Pre-Treated	0.701	0.546	0.899	
EDSS score at baseline				**<0.0001**
1 – 1.5 (reference)	–	–	–	
2 – 2.5	1.476	1.003	2.174	
3 – 3.5	3.155	2.174	4.579	
4 – 4.5	3.720	2.509	5.516	
5 – 5.5	4.523	2.993	6.974	
6 – 6.5	5.263	3.505	7.605	
≥ 7	13.547	7.576	24.225	
Relapses 1 year prior				0.16
0 (reference)	–	–	–	
1	1.163	0.939	1.441	
> 1	1.239	0.993	1.545	

DMT: disease-modifying therapy. EDSS: Expanded disability status scale.

Table 5
Reported adverse events.

Reported adverse event	Number reported	%	Number of patients with AE	Proportion of patients (% of total)
Total	486	100.0	365	15.1
Cephalalgia	368	75.7	253	10.4
Unspecified, infusion-related	42	8.6	41	1.7
Unspecified	18	3.7	18	0.7
Respiratory tract infections	14	2.9	12	0.5
Urinary tract infections	12	2.5	10	0.4
Influenza-like symptoms	≤3	≤0.1	≤3	≤0.1
Post-zoster neuralgia	≤3	≤0.1	≤3	≤0.1
Progressive multifocal leukoencephalopathy	≤3	≤0.1	≤3	≤0.1
Toxic liver disease	≤3	≤0.1	≤3	≤0.1
Depression	≤3	≤0.1	≤3	≤0.1
Fever	≤3	≤0.1	≤3	≤0.1
Myalgia	≤3	≤0.1	≤3	≤0.1
Stomatitis/Candida-associated stomatitis	≤3	≤0.1	≤3	≤0.1
Alopecia	≤3	≤0.1	≤3	≤0.1
Cardiac arrhythmia	≤3	≤0.1	≤3	≤0.1
Conjunctivitis	≤3	≤0.1	≤3	≤0.1
cough	≤3	≤0.1	≤3	≤0.1
diarrhea	≤3	≤0.1	≤3	≤0.1
Idiopathic thrombocytopenic purpura	≤3	≤0.1	≤3	≤0.1
Insomnia	≤3	≤0.1	≤3	≤0.1
Lung cancer	≤3	≤0.1	≤3	≤0.1
Macula edema	≤3	≤0.1	≤3	≤0.1
Malaise and fatigue	≤3	≤0.1	≤3	≤0.1
Nausea and vomiting	≤3	≤0.1	≤3	≤0.1
Swollen mucous membranes	≤3	≤0.1	≤3	≤0.1

AE: Adverse event.

Denmark, with suspected clinical activity triggering additional scans, limiting the potential for missingness due to confounding. Contrarily, patients with disease activity on MRI may be overrepresented. Despite this, we observed low occurrence of activity.

The observed low on-treatment disease activity was also reflected in the causes for discontinuation, with only 9% of total discontinuations being reported as due to disease activity. This was even lower in later epochs, supporting that changing patient characteristics are likely the main driver of the observed decrease in relapse rate in more recent epochs. Conversely, the most common cause for discontinuation was due to JCV antibodies (41%). Adverse events as a cause for discontinuation constituted around 10%, similar to pregnancy-related causes and occurrence of natalizumab antibodies. These findings are consistent with findings from other observational cohorts (Auer et al., 2021; Butzkueven et al., 2020).

The proportion of patients with registered adverse events was 14%. The vast majority was due to cephalalgia, which was also the most

frequent side effect in AFFIRM (Polman et al., 2006). Three or fewer cases of PML were registered (0.1% of patients), which is lower than reported elsewhere (Butzkueven et al., 2020; Foley et al., 2020). This may be due to lower capture in the DMSR, but also vigilance in clinics with regular measurement of JCV antibodies, and a restrictive selection scheme, excluding patients previously treated with cytostatic therapies or with JCV-positivity. While we cannot determine the seriousness of adverse events based on our data, the overall incidence of adverse events was low. A proxy for severity of adverse events may be the incidence of adverse events leading to discontinuation, which was low.

In this study, we present data from 2424 patients treated with natalizumab. The data represent a nationwide cohort, capturing virtually every patient treated in Denmark. The mandatory data collection performed at every clinical visit ensure uniform data capture at every clinical site. Combined, these factors provide good generalizability and validity of results. This study cohort of patients treated with natalizumab is among the largest published, making it less prone to random variation. Further, as natalizumab has been standard drug-of-choice in the high efficacy-tier in Denmark, and medicine is freely available, the patients fulfilling the drug indications are relatively unselected.

In conclusion, markers of disease activity remain low during long-term follow-up of patients treated with natalizumab in Denmark. We provide strong real-world evidence of efficient suppression of clinical relapses, EDSS worsening and radiological activity. Prescription patterns have changed over time, with more patients starting natalizumab earlier in the disease course, with shorter or no treatment history, and with lower accumulated disability levels. The most common cause for discontinuation is the appearance of JCV-antibodies, and discontinuation due to activity and adverse events were low. Registered adverse events were rare, with PML incidence lower than reported elsewhere.

CRediT authorship contribution statement

Mathias Due Buron: Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision. **Jeppe Romme Christensen:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision. **Luigi Pontieri:** Methodology, Software, Formal analysis, Visualization, Writing – review & editing, Data curation. **Hanna Joensen:** Writing – review & editing, Data curation. **Matthias Kant:** Investigation, Writing – review & editing. **Peter Vestergaard Rasmussen:** Investigation, Writing – review & editing. **Finn Sellebjerg:** Investigation, Writing – review & editing, Supervision. **Per Soelberg Sørensen:** Investigation, Writing – review & editing, Supervision. **Danny Bech:** Investigation, Writing – review & editing. **Melinda Magyari:** Conceptualization, Investigation, Writing – review & editing, Supervision, Funding acquisition, Resources.

Declaration of Competing Interest

MD Buron has received speaker honoraria from Novartis.

F Sellebjerg has served on scientific advisory boards for, served as consultant for, received support for congress participation or received speaker honoraria from Alexion, Biogen, Bristol Myers Squibb, H. Lundbeck A/S, Merck, Novartis, Roche and Sanofi Genzyme. His laboratory has received research support from , Merck, Novartis, Roche and Sanofi Genzyme.

M Magyari has served in scientific advisory board for Sanofi, Novartis, Merck, and has received honoraria for lecturing from Biogen, Merck, Novartis, Roche, Genzyme, Bristol Myers Squibb.

J Romme Christensen has received speaker honoraria from Biogen.

PV. Rasmussen has received speaker honoraria from TEVA, Biogen, Roche and Novartis, support for congress participation from Merck, Roche, Sanofi and TEVA, fees for serving on advisory boards from Merck, Roche, Novartis, Biogen, and Sanofi.

PS. Sorensen has received personal compensation for serving on advisory boards for Biogen, Merck, Novartis, Teva; on steering committees or independent data monitoring boards in trials sponsored by Merck, and Novartis; and has received speaker honoraria from Biogen, Merck, Teva, BMS/Celgene, and Novartis.

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Supplementary materials

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