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Original Research Paper

Long-term effect of natalizumab in patients with RRMS: TYSTEN cohort

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Abstract

Background: Data are needed on long-term effect of natalizumab (NTZ) in relapsing-remitting multiple sclerosis (RRMS).

Objectives: To evaluate the time of onset of secondary progressive phase in patients with an RRMS treated with NTZ and to investigate predictive factors.

Methods: TYSTEN is an observational study. Patients starting NTZ between 2007 and 2012 were included and followed up until October 2018. Relapses, Expanded Disability Status Scale (EDSS) scores, and results of brain magnetic resonance imaging (MRI) were collected each year. Data were used to estimate the cumulative probability of several poor outcomes such as secondary progressive multiple sclerosis (SPMS) conversion, EDSS worsening, EDSS 4.0, and EDSS 6.0.

Results: 770 patients were included. The mean follow-up duration was 97 months and the mean time exposure to NTZ was 66 months. At 10 years, the cumulative probability of SPMS was 27.7%. Predictive factors for poor outcomes were a ⩾1-point increase in EDSS score from baseline, new T2 lesion or T1 gadolinium-enhancing lesion, the occurrence of relapse at 1 or 2 years and No Evidence of Disease Activity (NEDA-3; no relapse, no new T2 or T1 gadolinium-enhancing lesions, no progression) was a protective factor.

Conclusion: In our cohort of patients treated with NTZ, poor outcomes were infrequent and are driven by disease activity.

Keywords: relapsing-remitting multiple sclerosis, secondary progressive multiple sclerosis, natalizumab, long-term, observational study

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Introduction

Multiple sclerosis (MS) is a complex disease of the central nervous system characterized by an inflammatory phase with acute multifocal demyelination followed by a degenerative phase with progressive clinical disability. The natural history of MS is now well described. Previous observational studies showed that half of the relapsing-remitting multiple sclerosis (RRMS) patients need a support to walk (Expanded Disability Status Scale score of 6.0 (EDSS 6.0)) after 23 years.[1] In the same way, half of the patients develop a progressive course (secondary progressive multiple sclerosis (SPMS)) after 19 years.[2]

Since the mid-1990s, the development of disease-modifying treatment (DMT) has had a high impact on relapse, but a moderate impact on progressive course with a median time from disease onset to SPMS of 23 years and to EDSS 6.0 of 31 years.[3]

Currently, one of the most effective treatments in RRMS is natalizumab (NTZ). By significantly reducing the annualized relapse rate (ARR) and the number of new T2 lesions on magnetic resonance imaging (MRI), NTZ efficiency led to the development of a new concept in MS: no evidence of disease activity (NEDA-3).[4–6] However, long-term data with NTZ are needed.

At the onset of MS, several predictive factors for poor evolution at the long-term are clearly defined as the ARR during the first 2 years of MS and the time to introduce a DMT.[7,8] However, it is also necessary to identify early predictive factors after treatment

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initiation as disease activity (relapse, new lesions, disability worsening) affecting the long-term disease course.

The aim of this real-life observational study was to evaluate the proportion of RRMS patients developing SPMS and a severe irreversible disability in a cohort of RRMS patients treated with NTZ on the long-term and to look for early predictive factors.

Methods

Patients

TYSTEN (TYSabri TEN years) is a retrospective observational study realized in two centers in France from two regions (Alsace and Nord-Pas-de-Calais) between April 2007 and September 2018. Inclusion criteria were an RRMS diagnosis established by Poser's classification before 2001[9] and by McDonald's classification after 2001,[10,11] an age ⩾ 18 years and to start NTZ (300 mg IV per 4 weeks) between April 2007 (date of the French approval for NTZ) and December 2012 after failure of a first-line therapy as a relapse on previous therapy or two serious relapses (multifocal or with sequelae) in the year. Patients who had not received at least three infusions of NTZ were excluded.

Outcome measures and assessments

Clinical visit was every 6 months in each center and data were collected, throughout the follow-up and independently of therapy status, directly in each center for patients followed by a physician from the center or in medical practice for patients followed by a private physician. Collected data were number of relapses, brain MRI activity (new lesion, gadolinium-enhanced lesion), and treatment. EDSS score was collected at least each year in the absence of relapse. Relapses within the first 3 months were not collected because NTZ was considered as not yet effective. For the period of washout after NTZ discontinuation, the practice was similar to the two centers with a washout of 1 month to begin a new treatment, except for fingolimod, for which the washout was 3 months in 2010 and 1 month from 2011.

The endpoints were the onset of SPMS (cumulative probability, time to convert, and predictive factors), the time to reach irreversible EDSS 4.0 and EDSS 6.0, EDSS worsening, treatment failure, MS activity (NEDA-3), and safety.

A clinical relapse was defined as new or recurrent neurological symptoms without fever, lasting at least 24 h, and followed by a period of 30 days of improvement or stability.

The irreversibility of disability was defined by EDSS score equal to or higher than the initial score 48 weeks later and for all subsequent scores during the follow-up.

SPMS was defined by modified criteria from proposed by Lorscheider et al.:[12] EDSS score ⩾ 4.0, progression of 1-point EDSS if EDSS ⩽ 5.5 or 0.5-point if EDSS ⩾ 6.0 in the absence of relapse, and progression confirmed over ⩾ 48 weeks. Although Pyramidal SF score is included in criteria proposed by Lorscheider, it was not used in our definition of SPMS because it was not systematically collected.

EDSS worsening was defined as a ⩾1-point increase in EDSS score from the baseline that was confirmed 48 weeks later and for all following scores.[13]

NEDA-3 corresponded to the absence of relapse, progression (defined as ⩾1.5-point EDSS if EDSS = 0, ⩾1-point EDSS if EDSS ⩽ 5.5, or ⩾0.5-point if EDSS ⩾ 6.0), or new T2 hyperintense lesions or T1 gadolinium-enhancing (T1-Gd) lesions on brain MRI.

Treatment failure was defined as NTZ discontinuation for disease activity or progression according to the physician.

To identify predictive factors affecting disease evolution, we recorded at 1 and 2 years of follow-up: occurrence of relapse, MRI worsening, a ⩾1-point increase in EDSS score from the baseline, and the exposure time to NTZ. MRI worsening was defined as a new T2 hyperintense lesion or T1 gadolinium-enhancing (T1-Gd) lesion on brain MRI. The exposure time to NTZ was divided into four groups as follows: no discontinuation, discontinuation within 2 years, discontinuation between 2 and 4 years, and discontinuation after 4 years.

Standard protocol approvals, registrations, and patient consents

This study was approved by local ethics committee. All patients gave their consent to be included in the cohort.

Statistical analysis

Descriptive analyses were performed with mean values (standard deviations) and medians

Table 1. Baseline patients' characteristics at the inclusion of the TYSTEN cohort.

Patients' characteristics	Value
Number of patients	770
Number of women, *n* (%)	555 (72.1)
Age at onset MS, mean ± SD	29.1 ± 9.1
Age at onset NTZ, mean ± SD	37.1 ± 10.3
Disease duration in years, mean ± SD	8.2 ± 6.8
Number of relapse 1 year before NTZ, mean ± SD	2.0 ± 1.1
EDSS score, median (range)	3 (2–4.5)
Number of patients with ⩾9 T2 lesions, *n* (%)	679 (91.9)
Number of patients with T1-Gd lesions, *n* (%)	367 (49.7)
Type of last treatment, *n* (%)	
IFN/GA	638 (83.6)
IS	35 (4.6)
No prior treatment	90 (11.8)

EDSS: expanded disability status scale; IFN: interferon β; IS: immunosuppressive drug; SD: standard deviation; T1-Gd: T1 gadolinium-enhancing.

(inter-quartiles ranges). Cumulative probabilities to reach endpoints were analyzed in the whole cohort (on NTZ and after discontinuation) and in the on-therapy cohort.

For comparison between each year during the follow-up for ARR and EDSS score for patients on NTZ and after NTZ discontinuation, the normal distribution of data was tested by D'Agostino & Pearson normality test and Shapiro–Wilk normality test. If data were normally distributed, an analysis of variance (ANOVA) was used, and if not, a Kruskal–Wallis test (nonparametric test) was used.

The Kaplan–Meier method was used to estimate the cumulative probability of SPMS, EDSS worsening, EDSS 4.0, and EDSS 6.0 in the whole cohort and in the on-therapy cohort. To find predictive factors, an adjustment on centers, sex, age at onset of MS and NTZ, last treatment before NTZ initiation, baseline EDSS score (<3.0 and ⩾3.0), and number of relapses during the year before NTZ was realized using a frailty Cox model.

Patients with irreversible EDSS score of 4.0 or 6.0 at baseline were not included into the analysis of cumulative probabilities to reach these scores and into the frailty Cox model for these endpoints.

Data availability

Anonymized data will be shared on request from any qualified investigator.

Results

Descriptive statistics

In December 2012, 770 patients were included. Baseline characteristics are presented in Table 1. The mean time of the follow-up was 97.2 ± 28.1 months and the mean NTZ treatment duration of 66 months on NTZ (number of infusions, min.: 3, max.: 149). NTZ was discontinued in 60.3%, mainly for a positive John Cunningham virus (JCV) serology (26.3%) and most of the time for a JCV index > 1.5. The main treatment of substitution was fingolimod (48.0%). The patients' characteristics at the end of the follow-up are summarized in the Table 2.

Relapses, EDSS score, and NEDA-3

On NTZ, mean ARR decreased from 2.0 ± 1.1 at baseline to 0.39 ± 0.70 at 2 years, to 0.20 ± 0.46 at 5 years and to 0.05 ± 0.23 at 10 years, so a reduction of 80.5%, 90%, and 97.5%, respectively ($p < 0.0001$ for each one). ARR was strongly reduced to 1 year and decreased progressively during the follow-up (Figure 1(a)). The median time without relapse on NTZ was 30 (10–NA) months, and the cumulative probability to have a relapse at 10 years was 67.8% (Figure 2(a)). The EDSS score on NTZ was stable during the follow-up (Figure 1(c)). At 2 years, 52.4% of patients were in NEDA-3 (Figure 2(b)).

To avert a potential selection bias in the group NTZ discontinuation by inclusion of patients who discontinued NTZ for disease activity or progression, we

Table 2. Characteristics at the end of the follow-up.

Characteristic	Value
Time of follow-up in months, mean ± SD	97.2 ± 28.1
Time with natalizumab in months, mean ± SD	66.0 ± 37.0
Number of patients with EDSS worsening, *n* (%)	223 (29.0)
Number of patients with SPMS, *n* (%)	167 (21.7)
Number of patients with SPMS according to physician, *n* (%)	84 (10.9)
Number of patients reaching EDSS 4.0, *n* (%)	369 (47.9)
Number of patients reaching EDSS 6.0, *n* (%)	167 (21.7)
Number of PML, *n* (%)	9 (1.1)
Discontinuation of natalizumab, *n* (%)	
Yes	465 (60.3)
No	253 (32.9)
Stop then re-use of natalizumab	51 (6.6)
Reason for discontinuation, *n* (%)	
JCV serology	196 (26.3)
Adverse event	50 (6.7)
Pregnancy planning	47 (6.3)
Absence of effect (relapse or new T2 or T1-Gd lesion)	39 (5.2)
Diagnostic of SPMS by physician	37 (4.9)
Patient wish	28 (3.7)
Anti-natalizumab Ab	16 (2.1)
Pregnancy	14 (1.8)
Death	8 (1.0)
Other	3 (0.4)
Missing data	52 (6.7)
Treatment after natalizumab, *n* (%)	
Fingolimod	198 (48.0)
Fumarate	65 (15.7)
Interferon β	32 (7.7)
Glatiramer acetate	27 (6.5)
Cyclophosphamide	22 (5.3)
Mycophenolate	11 (2.6)
Mitoxantrone	8 (1.9)
Rituximab	5 (1.2)
Teriflunomide	4 (0.9)
Azathioprine	2 (0.4)
Biotin	2 (0.4)
Methotrexate	2 (0.4)
Alemtuzumab	1 (0.2)
No treatment before re-use of natalizumab	33 (8.0)

EDSS: expanded disability status scale; JCV: John Cunningham virus; PML: progressive multifocal leukoencephalopathy; SD: standard deviation; SPMS; secondary progressive multiple sclerosis; T1-Gd: T1 gadolinium-enhancing.

analyzed the ARR and the EDSS for only patients who discontinued NTZ for JCV reason. The number of relapses and the EDSS score were stable after NTZ discontinuation (Figure 1(b) and (d)). However, patients who were relapse free or in NEDA-3 at the last infusion of NTZ had a probability 1 year after to have a relapse of 29.2% and evidence of disease activity of 41.6% (Figure 2(b) and (d)).

Endpoint analysis: SPMS, EDSS worsening, EDSS 4.0, EDSS 6.0, and treatment failure

At the end of the follow-up, 167 patients (21.7%) converted to SPMS, 223 patients (29.0%) had EDSS worsening, 369 patients (48%) had an EDSS 4.0, and 167 patients (21%) had an EDSS 6.0 (Table 2). The cumulative probabilities were, respectively, 27.3%, 34.2%, 26.5%, and 18.1% for the whole cohort, and

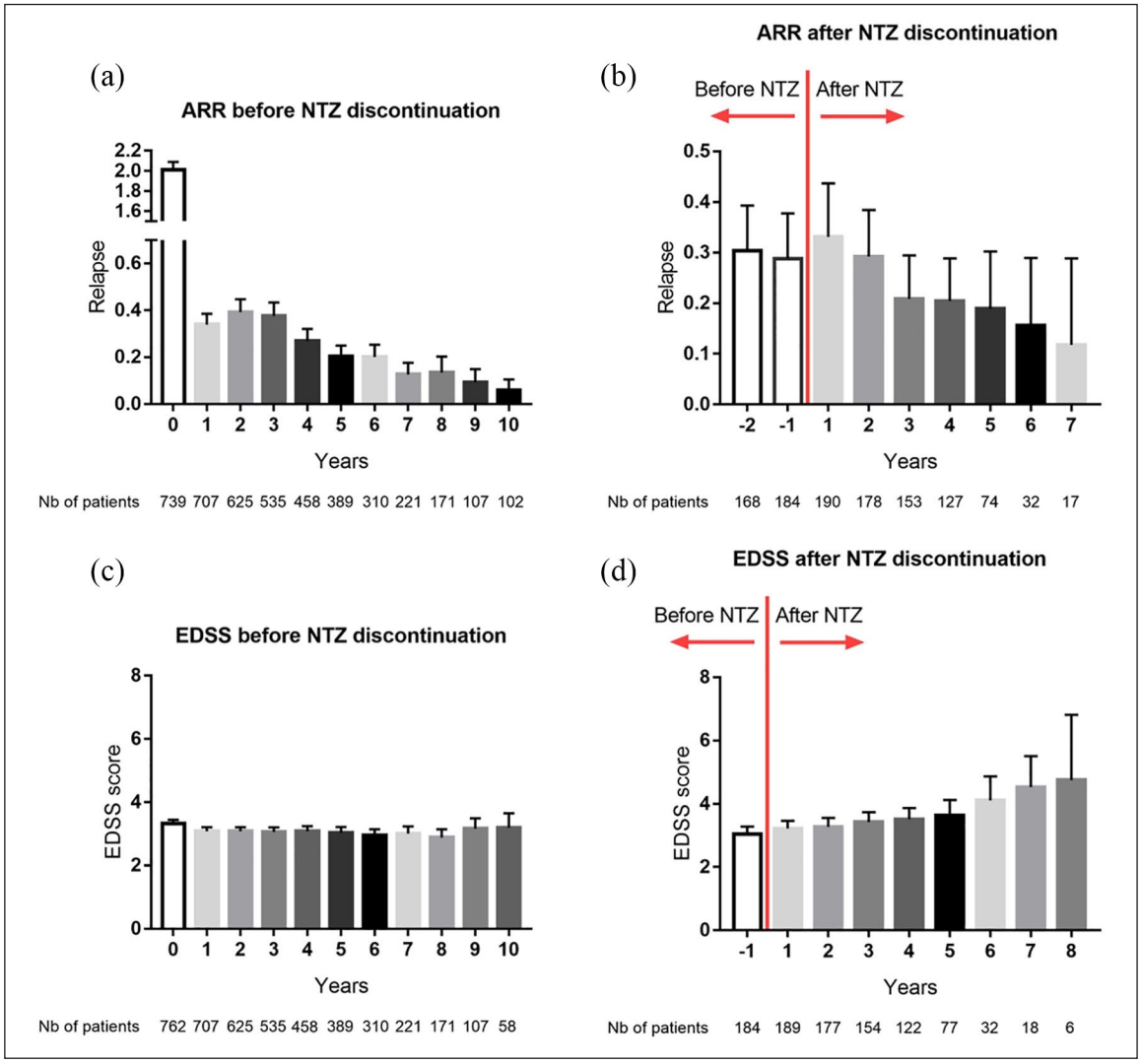

Figure 1. ARR and EDSS scores per year before and after natalizumab discontinuation: (a) ARR before NTZ discontinuation. After NTZ initiation, the relapse rate was significatively reduced compared to relapse rate before NTZ initiation ($p < 0.05$*). (b) ARR after NTZ discontinuation for JCV reason. Compared to the relapse rate before NTZ discontinuation, the relapse rate after NTZ discontinuation remained stable ($p > 0.05$*). (c) Mean EDSS score per year before NTZ discontinuation. Mean EDSS score was stable during the follow-up for patients with NTZ ($p > 0.05$*). (d) Mean EDSS score per year after NTZ discontinuation for JCV reason. Mean EDSS score was stable during the follow-up after NTZ discontinuation ($p > 0.05$*).
ARR: annualized relapse rate; EDSS: Expanded disability status scale; NTZ: natalizumab.
Error bars indicate 95% CIs.
*Kruskal–Wallis test.

23.7%, 30.4%, 25.1%, and 12.4% for the on-therapy cohort (Figure 3). The median time from the onset of MS to convert to SPMS and to reach an EDSS 6.0 was 28 and 34 years, respectively (Figure 3). NTZ was discontinued for treatment failure for 76/465 patients (16.3%).

For patients fulfilling SPMS criteria, only 58 (34.7%) were considered as SPMS by physicians. Disease duration before NTZ initiation was 10.6 ± 8.0 years. NTZ was discontinued for 130 (77.8%) patients, and among them, 46 (35.4%) had a relapse after NTZ cessation after a mean of 13.5 ± 16.4 months. The main treatment after NTZ discontinuation was fingolimod for 58 (44.6%) patients.

Predictive factors of disability

In the Cox model (Table 3), the strongest predictive factors for SPMS, EDSS 4.0, and EDSS 6.0 was a

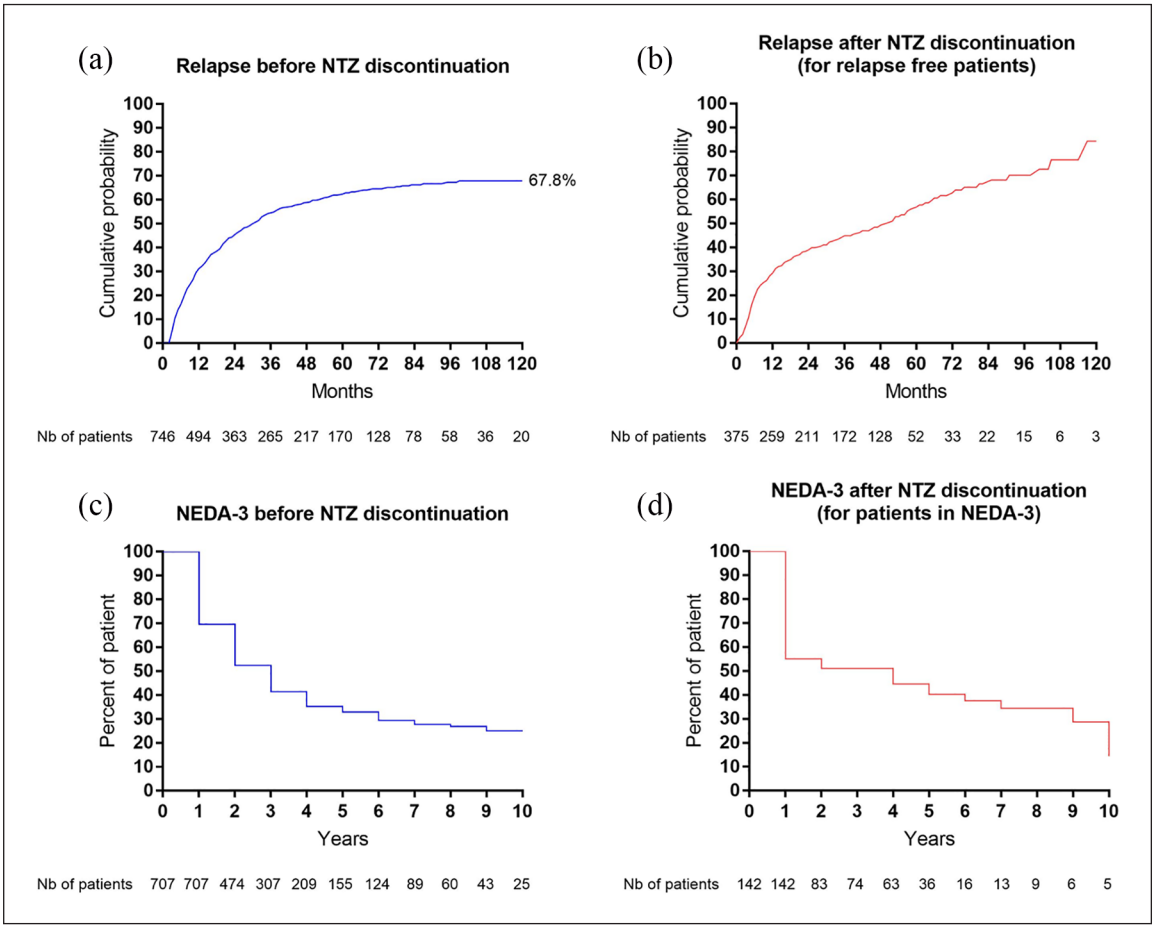

Figure 2. Cumulative probabilities of relapses and survival curves of patients in NEDA-3 before and after natalizumab discontinuation: (a) Cumulative probability of relapse with NTZ. (b) Cumulative probability of relapse after NTZ discontinuation for relapse free patients at NTZ discontinuation. (c) Survival curve of patients in NEDA-3 with NTZ. (d) Survival curve of patients in NEDA-3 after NTZ discontinuation for patients being NEDA-3 at NTZ discontinuation.
NEDA-3: no evidence of disease activity; NTZ: natalizumab.

⩾1-point increase in EDSS score from the baseline at the first or the second year of the follow-up in both cohorts (whole cohort and on-therapy cohort). In the same way, MRI worsening and the exposure time to NTZ were predictive factors and NEDA-3 is a protective factor for SPMS, EDSS worsening, EDSS 4.0, and EDSS 6.0 in both cohorts (Figure 4). The occurrence of relapse at the first or the second year was a protective factor for SPMS, but it was a risk factor in the sensitivity analysis on the 5–10 year period (Table 4). Among patients who converted to SPMS, 69/139 patients (50.4%) were relapse free within 2 years after NTZ initiation.

Age at NTZ initiation and the number of relapses one year before NTZ initiation were risk factors for treatment failure. Conversely, age at diagnosis of MS and T1-Gd lesion on baseline MRI were protective factors (Table 5).

Safety

Nine cases (1.1%) of progressive multifocal leukoencephalopathy (PML) were diagnosed with a median time of 47 months with NTZ (range 44–75). One of these patients was dead due to PML. Patients with PML were 39 (29.5–50) years old. All had a positive JCV serology.

Discussion

This real-life study, TYSTEN, confirms the efficacy of NTZ on inflammatory phase with an important reduction of ARR ⩾ 80% and many patients in NEDA-3, around 50% at 2 years. These results are consistent with pivotal studies which showed a reduction of ARR of around 68% compared to placebo[4] and 55% compared to interferon beta[5] and with previous real-life studies which showed a reduction of ARR of 73%–94% compared to pre-natalizumab levels.[14,15]

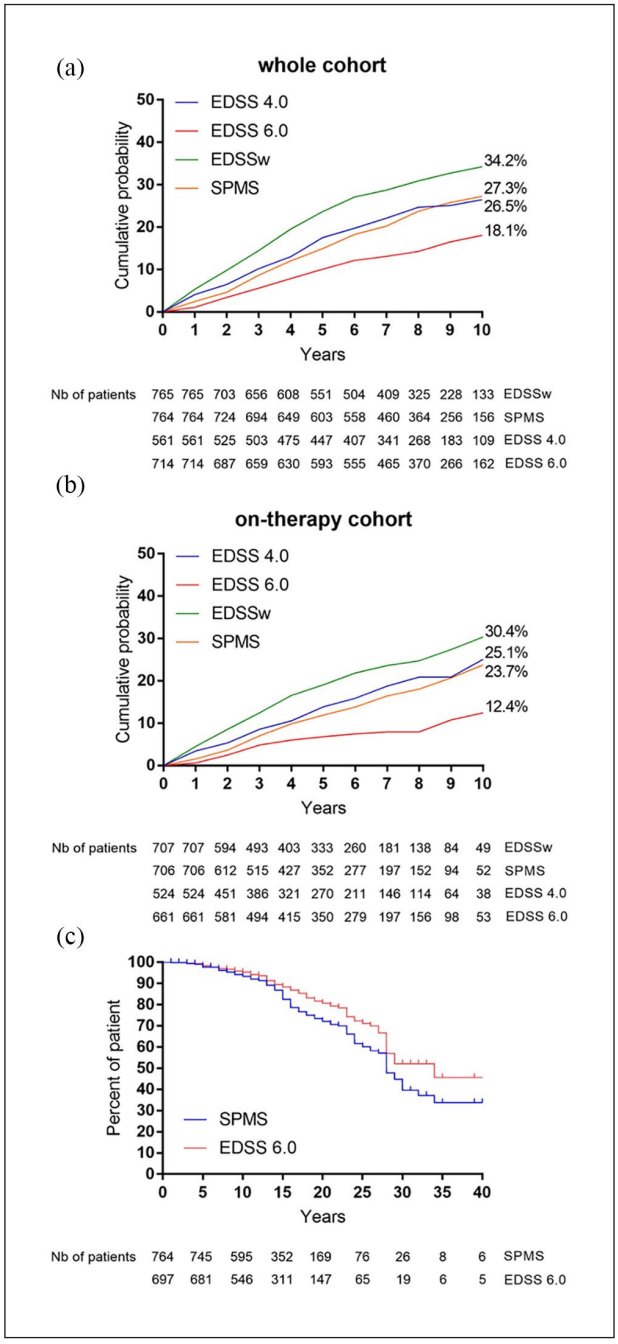

Figure 3. Cumulative probabilities of SPMS, EDSS worsening, EDSS 4.0 and 6.0 during the follow-up, and Kaplan–Meier curves to convert to SPMS and to reach EDSS 6.0 from the onset of multiple sclerosis: (a) Cumulative probabilities of EDSS worsening, SPMS, EDSS 4.0, and EDSS 6.0 during the follow-up in the whole cohort. (b) Cumulative probabilities to reach confirmed EDSS worsening, SPMS, EDSS 4.0, and 6.0 during the follow-up in the on-therapy cohort. (c) Kaplan–Meier curves to convert to SPMS and to reach EDSS 6.0 from the onset of multiple sclerosis in the whole cohort.

EDSS: expanded disability status scale; EDSSw: EDSS worsening; SPMS: secondary progressive multiple sclerosis.

SPMS was defined as EDSS score ⩾ 4.0, progression of 1-point EDSS if EDSS ⩽ 5.5 or 0.5-point if EDSS ⩾ 6.0 in the absence of relapse, and progression confirmed over ⩾48 weeks.

EDSS worsening was defined as either a ⩾1-point increase in EDSS score from the baseline that was confirmed 48 weeks later and for all following scores.

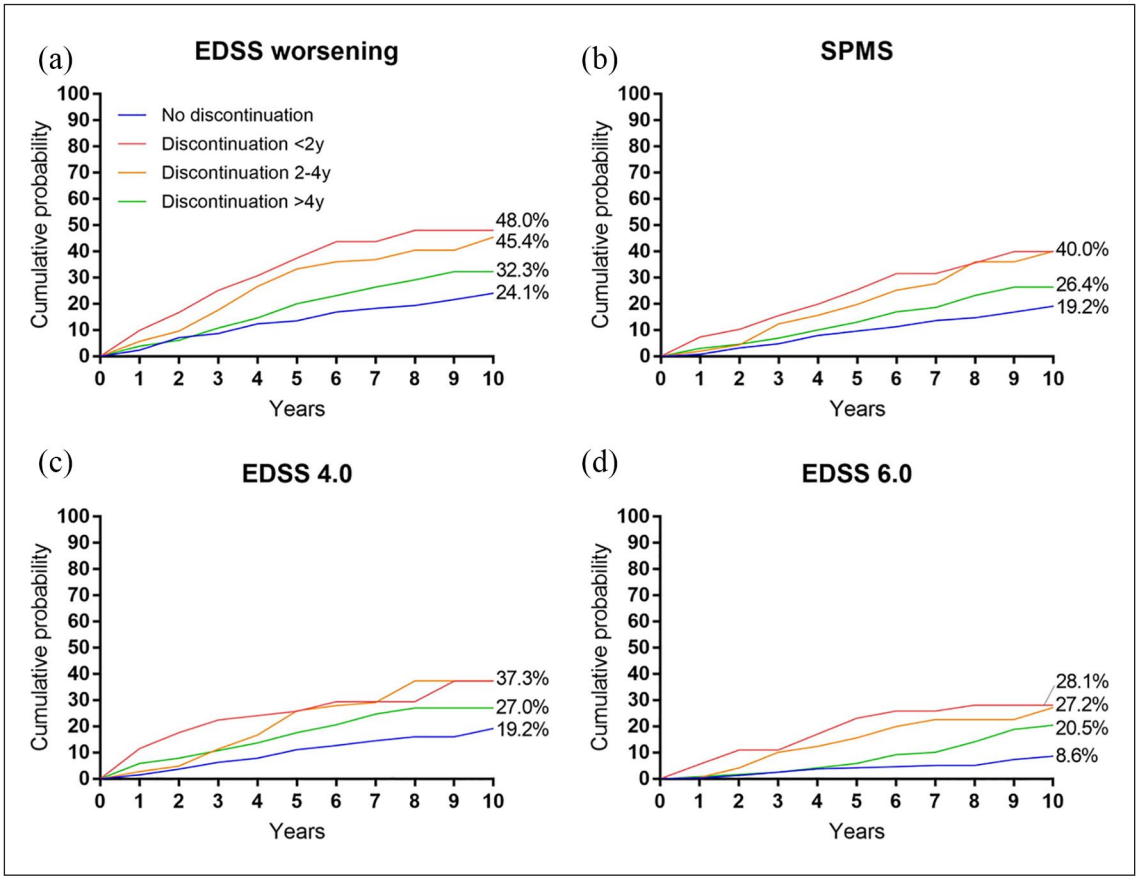

Figure 4. Cumulative probabilities of EDSS worsening, SPMS, and EDSS 4.0 and 6.0 according to the exposure time to NTZ. The exposure time to NTZ was divided into four groups as follows: no discontinuation, discontinuation within 2 years, discontinuation between 2 and 4 years, and discontinuation after 4 years. (a) Cumulative probability of EDSS worsening. (b) Cumulative probability of SPMS. (c) Cumulative probability to reach an EDSS 4.0. (d) Cumulative probability to reach an EDSS 6.0.
EDSS: expanded disability status scale; SPMS: secondary progressive multiple sclerosis.

The number of relapses during follow-up decreases progressively. It could be a long-term effect of NTZ or the effect of treatments used after NTZ or related to aging patients and is influenced by a phenomenon of regression to the mean.[16]

The mean time on NTZ is around 5.5 years, and at the end of the follow-up, 60% stopped the treatment. The main reason for discontinuation is linked to the risk of PML (26.3%) and is higher than in previous observational studies probably because seroconversion increases with time exposure.[17,18] Indeed, in Tysabri Observational Program (TOP), 1.3% of patients stopped NTZ for a positive JCV serology.[15] In our cohort, around 30% of patients had a relapse during the first years after NTZ cessation. In another study, the probability of relapse within the year after NTZ cessation was 45%.[19]

In our cohort, nine (1.1%) patients had a PML on NTZ, which seems to be similar to the incidence of NTZ-related PML in the most recent studies (2.0 to 4.3 per 1000 exposed patients).[20,21]

Median times from onset of MS to convert to SPMS and to reach an EDSS 6.0 were 28 and 34 years, respectively, and seem to be higher than previous studies[2,22] and similar to studies in the treatment era.[3,23] However, in our cohort, disease activity before NTZ seems to be higher than in previous studies and could participate in reducing the effect of NTZ. Moreover, we have used a modified version of SPMS criteria proposed by Lorscheider et al.,[12] which are more sensitive than previous criteria leading to identify patients with SPMS 3 years earlier on average. The comparison with previous cohorts is limited by modification of environmental factors like smoking,

Table 3. Hazard ratio of predictive factors for long-term clinical outcomes in the whole cohort and on-therapy cohort.

Endpoints	Variables	Whole cohort[a]									On-therapy cohort[b]					
		Predictive factors at baseline[c]			Predictive factors at 1 year[d]			Predictive factors at 2 years[e]			Predictive factors at 1 year[d]			Predictive factors at 2 years[e]		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
EDSS worsening		*n*=677			*n*=674			*n*=618			*n*=652			*n*=553		
	Time on NTZ															
	<2 years vs No discontinuation	2.69	1.18–6.14	**0.018**												
	2–4 years vs No discontinuation	2.07	2.00–2.14	**<0.001**												
	⩾5 years vs No discontinuation	1.55	1.23–1.95	**<0.001**												
	Relapse				1.22	0.76–1.96	0.41	1.23	0.88–1.72	0.22	1.34	0.82–2.19	0.25	1.50	1.50–1.50	**<0.001**
	New T2 or T1-Gd lesion				1.95	1.42–2.67	**<0.001**	4.94	2.26–10.79	**<0.001**	1.25	0.74–2.11	0.40	2.46	2.14–2.84	**<0.001**
	NEDA-3				1.97	1.66–2.33	**<0.001**	2.97	1.51–5.85	**0.002**	2.34	2.02–2.72	**<0.001**	2.37	1.78–3.16	**<0.001**
SPMS		*n*=674			*n*=674			*n*=636			*n*=652			*n*=571		
	Time on NTZ															
	<2 years vs No discontinuation	3.03	1.31–6.99	**0.009**												
	2–4 years vs No discontinuation	2.04	1.62–2.59	**<0.001**												
	⩾5 years vs No discontinuation	1.75	1.32–2.33	**<0.001**												
	Relapse				0.11	0.04–0.28	**<0.001**	0.33	0.16–0.72	**0.005**	0.31	0.27–0.35	**<0.001**	0.65	0.34–1.25	0.20
	EDSS worsening				7.91	4.70–13.35	**<0.001**	3.99	2.38–6.68	**<0.001**	8.36	3.35–20.91	**<0.001**	3.70	2.83–4.83	**<0.001**
	New T2 or T1-Gd lesion				1.62	0.90–2.88	0.11	1.53	0.96–2.42	0.07	2.13	2.07–2.20	**<0.001**	1.55	1.20–2.00	**<0.001**
	NEDA-3				1.29	1.20–1.40	**<0.001**	1.19	1.12–1.26	**<0.001**	1.13	0.91–1.39	0.27	1.13	0.93–1.38	0.21
EDSS 4.0		*n*=677			*n*=490			*n*=456			*n*=484			*n*=424		
	Time on NTZ															
	<2 years vs No discontinuation	2.08	1.63–2.65	**<0.001**												
	2–4 years vs No discontinuation	1.46	1.45–1.47	**<0.001**												
	⩾5 years vs No discontinuation	1.32	1.31–1.32	**<0.001**												
	Relapse				1.25	1.01–1.56	**0.045**	1.48	1.12–1.95	**0.006**	1.30	0.90–1.90	0.17	1.40	0.98–1.98	0.062
	EDSS worsening				10.05	7.91–12.77	**<0.001**	8.51	6.26–11.57	**<0.001**	8.38	8.11–8.66	**<0.001**	6.56	4.34–9.91	**<0.001**
	New T2 or T1-Gd lesion				2.76	1.50–5.08	**0.001**	1.58	1.38–1.81	**<0.001**	2.36	1.57–3.54	**<0.001**	1.40	1.29–1.51	**<0.001**
	NEDA-3				2.15	1.47–3.16	**<0.001**	1.82	1.55–2.15	**<0.001**	1.92	1.90–1.94	**<0.001**	1.82	1.50–2.21	**<0.001**
EDSS 6.0		*n*=677			*n*=626			*n*=601			*n*=611			*n*=543		
	Time on NTZ															
	<2 years vs No discontinuation	5.53	2.83–10.80	**<0.001**												
	2–4 years vs No discontinuation	2.92	1.79–4.77	**<0.001**												
	⩾5 years vs No discontinuation	2.80	2.07–3.76	**<0.001**												
	Relapse				1.04	0.66–1.64	0.86	0.91	0.56–1.44	0.68	0.98	0.94–1.02	0.36	1.04	0.55–1.97	0.91
	EDSS worsening				6.58	3.71–11.65	**<0.001**	6.72	3.84–11.76	**<0.001**	8.04	6.08–10.64	**<0.001**	3.12	1.62–6.03	**<0.001**
	New T2 or T1-Gd lesion				2.08	1.03–4.17	**0.04**	6.23	2.27–17.05	**<0.001**	0.83	0.45–1.52	0.55	1.24	1.03–1.50	**0.024**
	NEDA-3				1.23	1.11–1.35	**<0.001**	3.88	1.44–10.47	**0.008**	1.24	0.86–1.78	0.25	4.36	1.17–16.29	**0.028**

EDSS: Expanded disability status scale; HR: hazard ratio; NEDA-3: no evidence of disease activity; NTZ: natalizumab; SPMS: secondary progressive multiple sclerosis; T1-Gd: T1 gadolinium-enhanced.
[a]Patients on NTZ and after discontinuation.
[b]Patients censored at the last NTZ infusion.
[c]Analysis of endpoints from year 1.
[d]Analysis of endpoints from year 2.
[e]Analysis of endpoints from year 3.
The significative values with $p<0.05$ are in bold.

Table 4. Hazard ratio of predictive factors for long-term clinical outcomes in 5–10 years period (sensitivity analysis).

Endpoints	Variables	Whole cohort[a]									On-therapy cohort[b]					
		Predictive factors at baseline[c]			Predictive factors at 1 year[d]			Predictive factors at 2 years[e]			Predictive factors at 1 year[d]			Predictive factors at 2 years[e]		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
EDSS worsening		*n*=483			*n*=483			*n*=483			*n*=312			*n*=312		
	Time on NTZ															
	<2 years vs No discontinuation	2.58	0.71–9.36	0.15												
	2–4 years vs No discontinuation	1.90	1.80–2.00	**<0.001**												
	⩾5 years vs No discontinuation	1.88	1.06–3.32	**0.03**												
	Relapse				1.22	0.76–1.96	0.41	1.14	0.94–1.38	0.18	1.36	1.05–1.75	**0.02**	1.81	1.60–2.05	**<0.001**
	New T2 or T1-Gd lesion				1.94	1.42–2.67	**<0.001**	1.17	0.89–1.55	0.27	2.21	2.01–2.44	**<0.001**	1.66	1.05–2.62	**0.03**
	NEDA-3				1.17	0.89–1.55	0.27	1.11	0.96–1.28	0.16	1.28	0.89–1.86	0.19	1.52	1.42–1.64	**<0.001**
SPMS		*n*=527			*n*=527			*n*=527			*n*=328			*n*=328		
	Time on NTZ															
	<2 years vs No discontinuation	2.91	1.43–5.92	**0.003**												
	2–4 years vs No discontinuation	2.33	2.25–2.42	**<0.001**												
	⩾5 years vs No discontinuation	1.95	1.90–2.00	**<0.001**												
	Relapse				1.28	1.22–1.36	**<0.001**	1.22	1.12–1.32	**<0.001**	1.18	1.01–1.37	**0.035**	1.67	1.67–1.68	**<0.01**
	EDSS worsening				2.90	1.92–4.36	**<0.001**	3.30	2.85–3.84	**<0.001**				3.28	0.48–22.37	0.23
	New T2 or T1-Gd lesion				1.58	0.38–6.57	0.53	1.49	0.98–2.28	0.062	0.98	0.14–7.02	0.98	1.47	1.32–1.63	**<0.001**
	NEDA-3				1.52	0.92–2.50	0.10	1.45	1.13–1.86	**0.004**	1.18	0.72–1.93	0.51	1.30	1.24–1.36	**<0.001**
EDSS 4.0		*n*=386			*n*=386			*n*=386			*n*=255			*n*=255		
	Time on NTZ															
	<2 years vs No discontinuation	1.45	0.58–3.61	0.42												
	2–4 years vs No discontinuation	2.35	1.57–3.53	**<0.001**												
	⩾5 years vs No discontinuation	2.06	1.34–3.15	**0.001**												
	Relapse				2.00	1.48–2.70	**<0.001**	2.14	1.09–4.19	**0.027**	3.40	2.65–4.35	**<0.001**	3.74	2.38–5.88	**<0.001**
	EDSS worsening				5.78	4.79–6.96	**<0.001**	7.54	3.56–15.95	**<0.001**	§			4.75	3.88–5.81	**<0.001**
	New T2 or T1-Gd lesion				3.28	2.01–5.35	**<0.001**	1.65	1.08–2.52	**0.021**	2.60	2.45–2.76	**<0.001**	2.37	1.94–2.91	**<<0.001**
	NEDA-3				2.54	1.80–3.57	**<0.001**	2.10	1.45–3.06	**<0.001**	3.26	2.69–3.94	**<0.001**	3.09	1.98–4.84	**<0.001**
EDSS 6.0		*n*=516			*n*=516			*n*=516			*n*=327			*n*=327		
	Time on NTZ															
	<2 years vs No discontinuation	7.07	3.11–16.16	**<0.001**												
	2–4 years vs No discontinuation	4.62	1.97–10.83	**<0.001**												
	⩾5 years vs No discontinuation	6.02	2.92–12.40	**<0.001**												
	Relapse				1.29	0.92–1.80	0.14	0.93	0.47–1.82	0.83	2.10	1.27–3.47	**0.004**	1.42	1.25–1.63	**<0.001**
	EDSS worsening				3.62	2.67–4.91	**<0.001**	4.90	1.74–13.79	**0.003**	§			2.51	0.31–20.24	0.39
	New T2 or T1-Gd lesion				1.15	0.74–1.79	0.54	8.03	1.40–46.13	**0.019**	§			§		
	NEDA-3				1.15	0.88–1.51	0.29	1.00	0.61–1.65	1.00	1.97	1.16–3.34	**0.012**	1.24	1.05–1.48	**0.013**

EDSS: Expanded disability status scale; HR: hazard ratio; NEDA-3: no evidence of disease activity; NTZ: natalizumab; SPMS: secondary progressive multiple sclerosis; T1-Gd: T1 gadolinium-enhanced.
[a]Patients on NTZ and after discontinuation.
[b]Patients censored at the last NTZ infusion.
[c]Analysis of endpoints from year 1.
[d]Analysis of endpoints from year 2.
[e]Analysis of endpoints from year 3.
§Variable was removed because the model did not converge.
The significative values with $p<0.05$ are in bold.

Table 5. Hazard ratio of predictive factors for treatment failure.

Variables	HR	95% CI	*p*-value
	$n=712$		
Age at diagnosis of MS	0.97	0.96–0.97	**<0.001**
Age at NTZ onset	1.04	1.04–1.05	**<0.001**
Sex (male)	1.32	0.99–1.75	0.061
Baseline EDSS ⩾ 3	2.97	0.73–12.12	0.13
Number of relapses 1 year before NTZ	1.07	1.04–1.10	**<0.001**
Baseline MRI ± 9 T2 lesions (⩾9)	§		
Baseline MRI T1 T1-Gd lesions (⩾1)	0.56	0.39–0.80	**0.002**
Last treatment before NTZ			
IS vs IFN/GA	1.28	0.63–2.59	0.50
No prior treatment vs IFN/GA	0.28	0.11–0.75	**0.011**

EDSS: Expanded disability status scale; HR: hazard ratio; NEDA-3: no evidence of disease activity; NTZ: natalizumab; SPMS: secondary progressive multiple sclerosis; T1-Gd: T1 gadolinium-enhancing.
Treatment failure was defined as NTZ discontinuation by the physician for disease activity or progression.
§Variable was removed because the model did not converge.
The significative values with $p<0.05$ are in bold.

modifying independently the disease course.[24] The cumulative probabilities at 10 years to convert to SPMS, to have an EDSS worsening, and to reach an EDSS 4.0 or 6.0 were below 40%. In the TOP, for patients with NTZ at least 2 years, the cumulative probability of EDSS worsening at 5 years was 13.5%. In comparison, in our cohort, the cumulative probability of EDSS worsening at 5 years was 24.8% for patients with NTZ at least 2 years.[13]

Not reaching NEDA-3, MRI worsening, increased EDSS score, and to a lesser extent the occurrence of relapse were identified as predictive of disability at the long-term. The occurrence of relapse at the first or the second year was only a risk factor for SPMS in sensitivity analysis on the 5 to 10 year period, perhaps because a part of patients without relapse within 2 years of follow-up already begun to convert to SPMS. These patients with less inflammatory activity could have less response to NTZ.[25] Subject to survival bias, early NTZ discontinuation was a risk factor for poor outcomes. These results are consistent with studies on interferon beta.[26,27] In a recent study on a cohort of patients with clinically isolated syndrome, RRMS, and SPMS receiving DMTs or not, the occurrence at 1 year of two or more T1-Gd lesions or new infratentorial or spinal cord lesion was associated with the conversion to SPMS, EDSS score, and cognitive performance at 15 years.[28]

Interestingly, among the patients fulfilling SPMS criteria, some patients were not considered as converting to SPMS by physicians and were still with drugs acting on RR phase at the end of the follow-up. In the same way, some patients without relapse activity and who did not fulfill SPMS criteria had worsening insidious disability. These patients could have a transitioning form of SPMS. However, in our cohort, for a third of patients fulfilled SPMS criteria and discontinued NTZ, a relapse activity was recovered. This could be explained by the mechanism of action of NTZ acting only on the inflammatory status and not directly on degenerative process in old lesions.[29] Thus, in a part of patients with RRMS, although inflammatory process is still ongoing, an insidious disability worsening or silent progression could take place.[30,31]

Finally, these results suggest that inflammatory process precedes and could lead to neurodegenerative process with an overlap period.[30,32] Thus, these predictive factors for SPMS as increase of EDSS or MRI worsening could be important in the therapeutic decision-making. Indeed, for patients with these factors or with silent progression, the switch to treatment also acting on progression could be interesting.[33]

The main limitation of our study is the lack of a control group. Several studies used a historical control group, but this puts the risk of a Will Rogers phenomenon and the risk of confounding factors because there is no randomization.[34] Specific effect of each treatment after NTZ has not been evaluated because the main treatment after NTZ discontinuation was fingolimod and treatments usually given for progressive phases were introduced after the diagnosis of SPMS.

NTZ is effective on the inflammatory process, and the cumulative probability of SPMS conversion was

below 30% and of EDSS 6.0 was below 20%. Disease activity criteria are predictive factors for poor outcomes and could be useful for therapeutic decision-making at the stop of NTZ. These findings need to be confirmed in a larger and longer follow-up and to be compared with other second-line treatments.

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