

Original Article

Long-term effectiveness of natalizumab in secondary progressive multiple sclerosis: A propensity-matched study

Clara G. Chisari^{a,b}, Umberto Aguglia^c, Maria Pia Amato^{d,e}, Roberto Bergamaschi^f, Antonio Bertolotto^g, Simona Bonavita^h, Vincenzo Brescia Morraⁱ, Paola Cavalla^j, Eleonora Cocco^k, Antonella Conte^{l,m}, Salvatore Cottoneⁿ, Giovanna De Luca^o, Alessia Di Sapio^g, Massimo Filippi^{p,q,r,s,t}, Antonio Gallo^h, Claudio Gasperini^u, Franco Granella^v, Giacomo Lus^w, Davide Maimone^x, Giorgia Teresa Maniscalco^y, Girolama Marfia^z, Lucia Moiola^q, Damiano Paolicelli^{aa}, Ilaria Pesci^{ab}, Paolo Ragonese^{ac}, Marco Rovaris^{ad}, Giuseppe Salemi^{ac}, Claudio Solaro^{ae}, Rocco Totaro^{af}, Maria Trojano^{ag}, Marika Vianello^{ah}, Mauro Zaffaroni^{ai}, Vito Lepore^{aj}, Francesco Patti^{a,b,*}, on behalf of the Italian MS Register Study Group

^a Department "GF. Ingrassia"; Section of Neurosciences, University of Catania, Italy

^b UOS Sclerosi Multipla, AOU Policlinico "G. Rodolico-San Marco", University of Catania, Catania, Italy

^c Regional Epilepsy Centre, Great Metropolitan "Bianchi-Melacrino-Morelli" Hospital, Reggio Calabria, Italy

^d Department NEUROFARBA, Section Neurosciences, University of Florence, Florence, Italy

^e IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy

^f IRCCS Mondino Foundation, Pavia, Italy

^g Department of Neurology and Multiple Sclerosis Regional Referral Centre, AOU San Luigi Gonzaga, Orbassano, Turin, Italy

^h Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli" Naples, Italy

ⁱ Multiple Sclerosis Centre, University Federico II, Naples, Italy

^j Multiple Sclerosis Center, Department of Neuroscience and Mental Health, City of Health and Science University Hospital of Torino, Torino, Italy

^k Multiple Sclerosis Centre Binaghi Hospital, ATS Sardegna-University of Cagliari, Italy

^l Department of Human Neurosciences, Sapienza University of Rome, Italy

^m IRCCS Neuromed Pozzilli, Italy

ⁿ Department of Neurology, A.R.N.A.S. Civico, Palermo, Italy

^o Multiple Sclerosis Center, Neurology Clinic, Policlinico SS Annunziata, University of Chieti-Pescara, Chieti, Italy

^p Neuroimaging Research Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy

^q Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

^r Neurorehabilitation Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

^s Vita-Salute San Raffaele University, Milan, Italy

^t Neurophysiology Service, IRCCS San Raffaele Scientific Institute, Milan, Italy

^u Department of Neuroscience, UOC Neurology, San Camillo-Forlanini Hospital, Rome, Italy

^v Neurosciences Unit, Department of Medicine and Surgery, University of Parma, Parma, Italy

^w Department of Advanced Medical and Surgical Sciences, II Division of Neurology, Multiple Sclerosis Center, University of Campania "L. Vanvitelli", Naples, Italy

^x Centro Sclerosi Multipla, UOC Neurologia, Azienda Ospedaliera Cannizzaro, Catania, Italy

^y Multiple Sclerosis Center, Cardarelli Hospital, Naples, Italy

^z Multiple Sclerosis Clinical and Research Unit, Department of Systems Medicine, Tor Vergata University, Rome, Italy

^{aa} Department of Translational Biomedicine and Neurosciences University of Bari, A. Moro, Bari, Italy

^{ab} Centro Sclerosi Multipla Unità Operativa Neurologia, Azienda Unità Sanitaria Locale, Ospedale Di Vaio, Fidenza, Parma, Italy

^{ac} Unit of Neurology, Department of Biomedicine, Neurosciences and Advanced Diagnostics, Palermo University, Palermo, Italy

^{ad} IRCCS Don C. Gnocchi Foundation ONLUS, Milan, Italy

^{ae} Department of Rehabilitation, C.R.R.F. "Mons. L. Novarese", Loc. Trompone, Moncrivello, (VC), Italy

^{af} Demyelinating Disease Center, Neurology Unit, University of L'Aquila, L'Aquila, Italy

^{ag} School of Medicine, University "Aldo Moro", Bari, Italy

^{ah} OU Neurology, Cà Foncello Hospital, Treviso, Italy

^{ai} Multiple Sclerosis Center, ASST della Valle Olona, Ospedale di Gallarate, (VA), Italy

^{aj} Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy

* Corresponding author.

E-mail address: patti@unict.it (F. Patti).

<https://doi.org/10.1016/j.neurot.2024.e00363>

Received 8 March 2024; Accepted 12 April 2024

1878-7479/© 2024 Published by Elsevier Inc. on behalf of American Society for Experimental NeuroTherapeutics. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

ARTICLE INFO

Keywords:

Natalizumab

Interferon beta 1b

Secondary progressive multiple sclerosis

Disability progression

ABSTRACT

Treatment options for secondary progressive MS (SPMS) are limited, especially considering that the new drugs recently approved are licensed for actively relapsing patients. We aimed to compare the disability progression in a real-world cohort of SPMS patients treated with natalizumab (NTZ) or interferon beta-1b (IFN β -1b). This multicenter retrospective enrolled patients with a diagnosis of SPMS according to 2014 Lublin criteria, who received NTZ or IFN β -1b for at least 48 months between the 1st June 2012 and the 15th May 2018 at 33 Italian MS centers contributing to the Italian MS Registry NTZ or IFN β -1b. Confirmed Expanded Disability Status Scale worsening (CEW) and progression independent of relapse (PIRA) were evaluated. In order to correct for non-randomization, a propensity score matching of the groups was performed. Out of 5206 MS patients identified at the time of data extraction, 421 SPMS patients treated with NTZ (224 [53.2%] females, mean age 45.3 ± 25.4 years) and 353 with IFN β -1b (133 [37.8%] females, mean age 48.5 ± 19.8 years) were enrolled. After applying the matching procedure, 102 patients were retained in the NTZ group and 98 in the IFN β -1b group. The proportion of patients who reached the 48-month 1-point CEW was significantly higher in IFN β -1b compared to NTZ group (58.2% versus 30.4%, $p = 0.01$). The proportion of patients who developed PIRA at 48 months were significantly higher in IFN β -1b compared to NTZ (72.4% versus 40.2%, $p = 0.01$). EDSS before treatment initiation and SPMS duration were risk factors for disability progression in terms of PIRA (HR 2.54, 25%CI 1.67–5.7; $p = 0.006$ and HR 2.04, 25%CI 1.22–3.35; $p = 0.01$, respectively). Patients treated with IFN β -1b were 1.64 times more to likely to develop PIRA (HR 1.64, 25%CI 1.04–4.87; $p = 0.001$). Treatment with NTZ in SPMS patients showed more favorable disability outcomes compared to IFN β -1b with beneficial effects over 48 months.

Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS), affecting an estimated 2.0–2.5 million people worldwide [1,2]. The most common phenotype of MS is the relapsing-remitting (RRMS), in which clinical relapses are followed by recovery [3,4]. According to the studies about natural history of the disease, RRMS typically transits over time toward a secondary progressive (SP) phase, in which relapses become less frequent and disability insidiously progresses [3,4].

Although an increasing number of DMTs have become available for relapsing MS and several guidelines for the therapy of SPMS have been proposed, treatment options for progressive MS are limited, especially considering that the new drugs recently approved for SPMS are licensed for patients who are actively relapsing [5–8]. The first treatment approved by European and US regulatory agencies for secondary progressive MS (SPMS) was the recombinant interferon β -1b (IFN β -1b) [9]. However, a systematic review revealed that interferons are not effective in reducing the risk of disease progression in SPMS [10]; on the other hand, IFN β -1b treatment may induce a significant reduction in the risk of relapse, as measured by the proportion of patients experiencing clinical relapses and by the relapse rate during follow-up [10]. Therefore, IFN β -1b, as the most of the available DMTs, has mechanisms of action primarily involving the modulation of the peripheral immune system and do not efficiently target the neuroaxonal injury secondary to the disseminate inflammation [11]. Similarly, even highly effective anti-inflammatory therapies successfully reduce the frequency of relapse and MRI activity, but have minimal effects on disability accrual [12,13]. Contrarywise, it has been hypothesized that drugs acting within the CNS may provide clinically beneficial effects in progressive forms of MS [4].

Natalizumab (NTZ) is a humanized monoclonal antibody that selectively binds to the $\alpha 4$ -subunit of integrins expressed on the surface of human leukocytes [14]. Several studies have demonstrated that NTZ significantly reduced the annualized relapse rate (ARR), the risk of confirmed disability deterioration and the accumulation of new brain MRI lesions in RRMS [15–17]. Therefore, the rationale behind the possible use of NTZ in SPMS was provided by previous studies showing that NTZ was able to reduce levels of chemokines, such as CXCL13, osteopontin and neurofilaments, in the CSF of SPMS patients [18,19]. Indeed, these molecules are known to contribute to the formation and maintenance of meningeal B-cell aggregates, a crucial component of the pathophysiology of SPMS [20–22]. Furthermore, a recent open-label study of NTZ in patients with progressive MS (12 SPMS and 11 primary progressive MS) showed a beneficial effect, as reflected by the

levels of CSF osteopontin, suggesting that NTZ may reduce intrathecal inflammation and tissue damage by preventing the recruitment of peripheral immune cells into the CNS [23]. However, evidences that NTZ may prevent or slow the sustained progression of disability in SPMS are currently lacking. Indeed, the 2-year randomized placebo-controlled, double-blind, study with an optional 2 year open-label extension (ASCEND) investigated the effect of NTZ on disability independent of relapse in SPMS, but it failed to demonstrate a significant reduction of disability progression (primary outcome) [24]. Therefore, the debate around starting or continuing NTZ therapy in progressive MS patients, particularly in those with worsening disability unrelated to clinical relapse, is still unresolved and warrant further studies.

On this background, we aimed to compare the disability progression risk in a real-world SPMS cohort of patients treated with NTZ and IFN β -1b from 33 Italian MS centers contributing to the Italian MS Registry.

Materials and methods

Study population

This multicenter retrospective study aimed to compare the risk of disability progression in SPMS patients treated with NTZ or IFN β -1b. Patients enrolled in this study received treatment between the 1st June 2012 and the 15th May 2018 at 33 Italian MS centers contributing to the Italian MS Registry [25]. Demographics and clinical data were retrospectively collected from the Italian MS Registry. The study was approved by the Policlinico-Vittorio Emanuele (Catania 1, Italy) Ethics Committee (n 37/2015/PO). Ethical committee approval was obtained from each individual institution.

Inclusion criteria were: 1) diagnosis of SPMS according to Lublin criteria [1] at the time of NTZ or IFN β -1b initiation; 2) treatment with NTZ 300 mg every month endovenously (e.v.) or IFN β -1b 0.25 mg (8MIU) every other day subcutaneously (s.c.); 3) treatment with NTZ or IFN β -1b continuously administered for at least 48 months; 4) availability of at least four Expanded Disability Scale (EDSS) scores and information on relapses documented for at least 48 months during NTZ or IFN β -1b treatment; 4) at least three MRI evaluations within 48 months during NTZ or IFN β -1 treatment. We excluded patients lacking of clinical and MRI data.

Outcomes

In order to evaluate the disability progression during treatment, EDSS evaluations and MRI data were acquired at baseline (within ± 6 months

from treatment initiation), at 12 ± 3 (T12), 24 ± 3 (T24), 36 ± 3 (T36) and 48 ± 3 (T48) months, after NTZ or IFNb-1b initiation.

The confirmed EDSS worsening (CEW), defined as an increase of ≥ 1.0 points if baseline EDSS was ≤ 5.5 points or an ≥ 0.5 -point increase if baseline EDSS was > 5.5 points that was confirmed at T12, T24, T36 and T48, was calculated [26,27].

Moreover, progression independent of relapse (PIRA) was evaluated at each time point. PIRA was defined as a ≥ 12 week confirmed disability progression; this last is referred to as a worsening of 1 point on the EDSS in patients with a baseline EDSS between 3.0 and 5.0 or a 0.5 step in EDSS in patients with a baseline EDSS ≥ 5.5 in the absence of relapse. According to PIRA definition, the relapse-free interval was calculated for a period of at least 12 consecutive months [28]. A clinical relapse was defined as occurrence of new signs or symptoms or exacerbation of existing one persisting for at least 24 h, in the absence of concurrent illness or fever, and occurring at least 30 days after a previous relapse [29]. Moreover, relapse data were recorded in the Italian MS Registry when reported by patients, and, as part of routine clinical practice, the clinical information were recorded with real time or near-real time data entry in relation to the neurological evaluation.

Active SPMS disease was defined by the presence of active disease within the 24 months before the treatment initiation, of clinical relapses and/or imaging features of inflammatory activity (new or enlarged T2 lesions and/or contrast-enhancing T1 lesions) [4,30]. MRI activity was defined by presence of at least one contrast-enhancing T1 lesion (CELTs) or the development of at least 1 new or enlarging T2 lesions in comparison to the previous MRI.

Statistical analysis

Statistical analysis was performed using STATA® 18.0 software (Stata-Corp LP, College Station, US) [31]. In descriptive analyses, continuous variables were summarized as mean and standard deviation (SD) or median and interquartile range (IQR), while categorical variables were expressed as percentages.

To minimize the imbalance between the groups, patients were 1:1 propensity score matched for baseline covariates at the time of the treatment (NTZ/IFNb-1b) initiation. The multivariable logistic regression model included the following covariates: sex, age, age at time of SP conversion, SP phase duration, relapses before DMT start (yes/no), EDSS before DMT start. We also matched patients on the basis of propensity score using nearest-neighbor matching without replacement, a caliper of 0.1, and a variable matching ratio of 1:5. To examine the quality of the match, we calculated the standardized difference, which does not depend on sample size. The match was considered successful if the standardized difference was < 10 for the majority of matching factors. A comparison of baseline variables between groups was performed using standardized mean difference, with a difference of less than 0.20 considered as an acceptable balance. For each analysis, the procedure for propensity score matching included only patients for whom outcome data were available during the relevant follow-up period of the analysis.

After assessing normality of data distribution, treatment outcomes were compared between the propensity score-matched patients with Student's t-test for parametric variables and nonparametric statistics for distribution of data deviated from normality. The association between two quantitative variables was performed through Pearson correlation coefficient or Spearman correlation coefficient, depending on the data distribution. Analysis of variance (ANOVA) was also applied to test main and interactive effects among the different time points (baseline, T12, T24, T36, and T48). Bonferroni test was used to correct for multiple post hoc pairwise comparisons.

Time to PIRA was estimated by Kaplan-Meier analysis and proportions of patients who developed PIRA were compared between the groups with Log-rank test censored at each time points. The variables significantly ($p < 0.15$) related with time to PIRA on univariate analysis were included in multivariate model. Multivariable Cox proportional hazards models were used to identify demographic and clinical variables significantly and independently associated with the outcome. Possible predictors ($p < 0.1$, uncorrected, at univariable analysis) entered the multivariable analysis. In order to evaluate the stability of the subsets and prevent overfitting, we applied the least absolute shrinkage and selection operator (LASSO) within the framework of survival Cox models, regressing each outcome on the whole set of selected features. This model selected the optimal value of the tuning parameter (λ), according to the within-1-standard-error rule from the minimum partial likelihood reached in a tenfold cross-validated (CV) scheme and, thus, controlling the amount of penalty and promoting variable selection. The null hypothesis was rejected if $p < 0.05$ (also an indicator of statistical significance). The adjusted hazard ratios (HRs) and their 95% CI were used to interpret the final model. A two-sided p-value of < 0.05 was considered as statistically significant.

Results

Out of 5206 MS patients identified with NTZ therapy in the Italian MS Registry at the time of data extraction, 421 SPMS patients treated with NTZ (224 [53.2%] females, mean age 45.3 ± 25.4 years) and 353 with IFNb-1b (133 [37.8%] females, mean age 48.5 ± 19.8 years) met the inclusion criteria and were enrolled (Fig. 1).

Patients receiving NTZ were younger with a higher percentage of females. Moreover, NTZ group had shorter SPMS phase duration, and a higher number of previous DMTs than patients starting with IFNb-1b. Number of relapses at MS diagnosis and of T1 brain lesions before treatment initiation were higher in IFNb-1b group compared to NTZ. Detailed baseline characteristics are illustrated in Tables 1–2.

Before matching procedure, a binary logistic regression in the total patient cohort was performed in order to assess the risk for PIRA under treatment. Higher EDSS before starting treatment and age at onset were found independently associated with a higher risk for PIRA (HR 2.61, 25% CI 1.14–5.32; $p = 0.001$; HR 1.32, 25% CI 1.04–5.28; $p = 0.01$, respectively).

After applying the nearest matching procedure, 102 patients were retained in the NTZ group and 98 in the IFNb-2b group. At each time

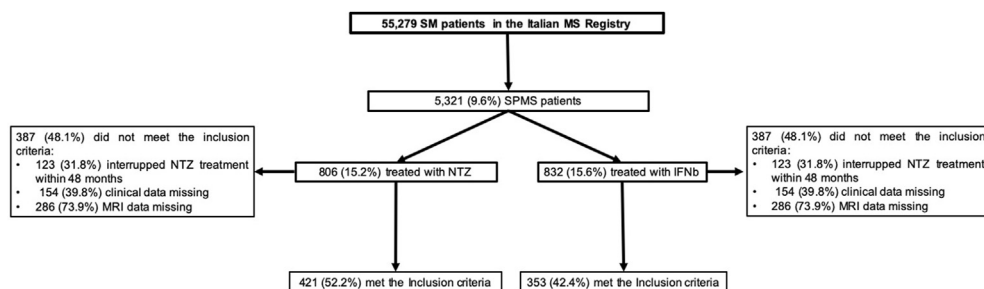


Fig. 1. Flow-chart of patients' distribution. IFNb-1b: interferon beta 1b; NTZ: natalizumab, SPMS: secondary progressive multiple sclerosis.

Table 1

Demographical and clinical characteristics of the cohort before and after the propensity score matching.

N (%)	Before matching			After matching		
	NTZ N. 421	IFN-1b N. 352	SMD	NTZ N. 102	IFN-1b N. 98	SMD
Female (%)	224 (53.2)	133 (37.8)	0.87	64 (62.7)	63 (64.3)	<0.1
Age (years) ^a ; mean ± SD median (range)	45.3 ± 25.4 48 (33–66)	48.5 ± 19.8 52 (42–68)	0.72	46.1 ± 27 49 (36–66)	47.9 ± 21.2 50 (42–68)	<0.1
Age at onset (years); mean ± SD median (range)	34.7 ± 9.5 38 (24–51)	38.0 ± 11.4 42 (35–53)	1.19	35.4 ± 12.6 40 (26–51)	37.4 ± 15.8 41 (35–49)	<0.1
Age at treatment initiation (years); mean ± SD median (range)	41.1 ± 28.3 42 (29–61)	49.5 ± 29.1 51 (44–66)	1.23	41.7 ± 22.5 42 (32–61)	42.5 ± 20.5 43 (44–61)	<0.1
MS disease duration (months) ^a ; mean ± SD median (range)	104.3 ± 61.3 95 (41–171)	109.6 ± 55.3 101 (52–185)	<0.1	105.0 ± 65.5 94 (41–171)	108.3 ± 57.8 100 (52–178)	<0.1
SPMS duration (months) ^a ; mean ± SD median (range)	48.3 ± 22.6 52 (43–70)	55.3 ± 37.9 58 (50–78)	1.06	49.5 ± 27.4 52 (43–70)	50.7 ± 21.5 51 (50–71)	<0.1
Number of patients with clinical and/or MRI activity; n (%) ^b	252 (59.9)	123 (34.9)	1.23	52 (51)	34 (34.7)	<0.1
EDSS at MS diagnosis; mean ± SD median (range)	2.5 ± 1.8 2.0 (1.0–4.5)	2.4 ± 1.6 2.5 (1.5–5.5)	<0.1	2.6 ± 2.0 2.0 (1.0–4.5)	2.4 ± 1.6 2.5 (1.5–5.5)	<0.1
EDSS at the time of treatment initiation; mean ± SD median (range)	4.8 ± 2.8 4.5 (3.5–7.0)	4.7 ± 3.6 4.5 (3.5–7.5)	<0.1	4.9 ± 3.1 4.5 (3.5–7.0)	5.0 ± 3.5 4.5 (3.5–6.5)	<0.1
N. of relapses at MS diagnosis; mean ± SD median (range)	1.3 ± 1.1 1.0 (1–5)	1.9 ± 1.3 2.0 (1–7)	0.87	1.6 ± 1.2 1.0 (1–3)	1.7 ± 1.4 1.0 (1–6)	<0.1
N of NTZ doses; mean ± SD; median (range) ^a	34.9 ± 15.8 36 (8–55)	NA	NA	32.2 ± 12.1 34 (8–45)	NA	NA
N. of previous DMTs mean ± SD; median (range) ^b	3.1 ± 1.8 2 (0–5)	2.0 ± 1.7 1 (0–4)	0.96	2.9 ± 1.9 2 (0–5)	1.9 ± 1.6 1 (0–4)	0.94
Number of patients with MRI activity; n (%) ^b	54 (12.8)	35 (9.9)	<0.1	12 (11.8)	10 (10.2)	<0.1
Number of T2 brain lesions; mean ± SD; median (range) ^b	24.8 ± 16.4 26 (18–43)	26.5 ± 21.6 29 (22–46)	<0.1	25.0 ± 21.4 26 (18–43)	26.1 ± 19.9 28 (22–44)	<0.1
Number of T1 brain lesions; mean ± SD; median (range) ^b	9.9 ± 7.4 7 (5–21)	11.5 ± 8.3 10 (7–33)	0.96	9.7 ± 5.5 7 (5–21)	11.2 ± 7.9 9 (7–30)	<0.1
Number of T2 spinal lesions; mean ± SD; median (range) ^b	1.9 ± 1.7 1 (0–5)	2.0 ± 1.7 2 (0–9)	<0.1	1.8 ± 1.9 1 (0–5)	2.2 ± 1.9 2 (0–9)	<0.1
Number of brain/spinal CEL; mean ± SD; median (range) ^b	1.7 ± 1.5 1 (1–3)	1.9 ± 1.7 2 (1–6)	0.19	1.3 ± 1.8 1 (1–2)	1.5 ± 1.4 1 (1–4)	<0.1

CEL: contrast-enhanced lesions; EDSS: Expanded Disability Status Scale; IFN-1b: interferon beta 1b; MS: multiple sclerosis; NA: not applicable; NTZ: natalizumab; PML: progressive multifocal leukoencephalopathy; SD: standard deviation; SMD: standardized mean differences; SPMS: secondary progressive multiple sclerosis.

^a At data extraction.

^b Before starting NTZ or IFNb-1b treatment.

points, both treatment groups showed no significant changes in terms of EDSS characteristics compared to baseline. MRI data also showed that number of T2 and T1 lesions remained stable after 12, 24 and 48 months (Table 2).

The analysis of disability outcomes showed that, at 12, 24 and 36 months, NTZ and IFNb-1b showed similar values of CEW (24.5%, 30.4%, and 29.4% in NTZ group, 26.5%, 35.7% and 36.7% in IFNb-1b, respectively). The proportion of patients who reached the 48-month 1-point

CEW was significantly higher in IFNb-1b compared to NTZ group (40.2% versus 72.4%, $p = 0.01$) (Table 3).

Moreover, proportion of patients reaching PIRA at 12, 24 and 36 months were 13.7%, 16.6%, and 14.7% in the NTZ group, 17.3%, 26.5%, and 25.5% in the IFNb-1b group, respectively, with time to PIRA similar between the two groups (Long rank test, $p = 0.3$). The proportion of patients who developed PIRA at 48 months were significantly higher in IFNb-1b compared to NTZ (57.1% versus 29.4%, $p = 0.01$) (Fig. 2). Cox

Table 2

Clinical and MRI characteristics at the time of treatment initiation (baseline), after 12 (T12), 24 (T24), 36 (T36) and 48 (T48) months during NTZ and IFb-1b treatment.

N (%)	NTZ N. 102				IFN-1b N. 98			
	T12	T24	T36	T48	T12	T24	T36	T48
N. of patients with relapses; n (%)	5 (4.9)	3 (2.9)	3 (2.9)	1 (1)	3 (3.1)	3 (3.1)	1 (1)	1 (1)
EDSS; mean ± SD median (range)	4.1 ± 2.5 4.0 (3.5–7.0)	4.5 ± 1.9 4.0 (3.5–7.0)	4.2 ± 2.6 4.0 (3.5–7.0)	4.3 ± 1.8 4.0 (3.5–7.0)	4.6 ± 3.5 4.0 (3.5–7.5)	4.6 ± 2.5 4.0 (3.5–7.0)	5.0 ± 2.2 4.4 (4.0–7.0)	5.4 ± 2.9 4.5 (4.0–7.0)
Number of T2 brain lesions; mean ± SD median (range)	22.8 ± 13.7 25 (18–42)	24.6 ± 19.7 27 (19–47)	25.2 ± 20.6 27 (22–44)	25.1 ± 22.7 28 (21–49)	23.4 ± 19.2 26 (18–43)	25.2 ± 19.9 30 (19–50)	25.1 ± 18.3 30 (22–54)	27.2 ± 21.9 31 (23–57)
Number of T1 brain lesions; mean ± SD median (range)	10.2 ± 8.6 13 (10–22)	11.5 ± 9.1 13 (9–25)	11.7 ± 8.3 12 (10–25)	11.0 ± 9.8 13 (9–26)	10.6 ± 7.9 12 (11–24)	11.5 ± 9.6 13 (12–29)	11.1 ± 9.5 13 (12–29)	11.4 ± 9.9 13 (12–31)
Number of T2 spinal lesions; mean ± SD median (range)	2.2 ± 2.0 3 (2–6)	2.2 ± 1.9 3 (2–6)	2.2 ± 1.7 3 (2–7)	2.5 ± 2.1 3 (2–7)	2.3 ± 1.9 3 (2–8)	2.1 ± 2.1 3 (3–9)	2.0 ± 1.4 3 (3–9)	2.1 ± 1.5 3 (3–9)
Number of patients with CEL; n (%)	4 (3.9)	3 (2.9)	1 (1)	1 (1)	2 (2)	0	0	1 (1)

ARR: annualized relapse rate; CEL: contrast-enhanced lesions; IFN-1b: interferon beta 1b; NTZ: natalizumab; SD: standard deviation.

Table 3

Disability outcomes.

	NTZ N.102		IFN-1b N. 98		p value
	N	%	N	%	
12 months confirmed EDSS worsening	25	24.5	26	26.5	0.8
24 months confirmed EDSS worsening	31	30.4	35	35.7	0.6
36 months confirmed EDSS worsening	30	29.4	36	36.7	0.4
48 months confirmed EDSS worsening	41	40.2	71	72.4	0.01

EDSS: expanded disability status scale; IFN-1b: interferon beta 1b; NTZ: natalizumab.

analysis on the propensity matched data applying the LASSO showed that EDSS before treatment initiation and SPMS duration were risk factors for disability progression in terms of PIRA (HR 2.50, 25%CI 1.53–6.29; $p = 0.007$ and HR 2.11, 25%CI 1.43–3.59; $p = 0.009$, respectively) (see [Supplementary Table 1](#)). Patients treated with IFN-1b were 1.73 times more to likely to develop PIRA compared to NTZ (HR 1.73, 25%CI 1.06–4.36; $p = 0.004$). Results from the multivariable Cox proportional hazards model were presented in [Fig. 3](#). The survival curve for the risk of PIRA in patients treated with NTZ or IFN-1b is reported in [Fig. 4](#).

Discussion

This multicenter retrospective study suggests that treatment with NTZ, compared to IFN-1b, significantly reduces the long-term risk of disability worsening, measured by PIRA in SPMS patients.

Indeed, at 48 months, patients treated with NTZ showed significantly lower risk of 1-point CEW, as well as of PIRA, compared to those treated with IFN-1b. However, at 12 and 24 months, NTZ and IFN-1b showed similar values of 1-point CEW. Similarly, no statistical differences were found between NTZ and IFN-1b in the percentage of patients reaching PIRA at 12 and 24 months.

It is known that PIRA is the dominant driver of disability worsening in SPMS patients. According to a recent analysis on data from 23 Novartis MS clinical trials, plus their extensions, PIRA occurs early in the disease, even in patients successfully treated with highly effective DMTs with suppression of inflammation [32]. On the other hand, treatment with DMTs may delay the time to disability milestones by several years [32]. This may explain the initial beneficial effect of both therapies, NTZ and IFN-1b, on disability progression, as observed in our study during the first years of treatment.

Consistent with these data, the approval of IFN-1b for the treatment of SPMS was based on the results of pivotal phase 3 studies of IFN-1b versus placebo in patients with SPMS, in which the primary endpoint was the time to disability progression over 3 years [33,34]. The double-blind, parallel-group randomized 1:1 to placebo, trial demonstrated that IFN-1b was associated to a prolonged time to disability progression compared with placebo in both the prospective interim, and final analyses [33,35]. On the contrast, in another study, in which SPMS patients were randomized 1:1:1 to receive IFN-1b 0.25 mg s.c. administered, IFN-1b 160 µg/m² (body surface area) s.c., or placebo, the primary endpoint was not met at either dose of IFN-1b [34]. Although, according to more recent papers, treatment with IFN-1b failed to prevent disability progression over the medium term (3 years), limiting the window of opportunity for efficacy to the early and more inflammatory phase of the disease [10,36].

In the current literature, the effects of NTZ on disability progression were investigated in several studies, by using various outcome measures, with results not always satisfactory. Two retrospective studies have analyzed data from NTZ-treated SPMS patients who participated in the MS231 and MS102 studies [37–39]. A post-hoc analysis investigated the efficacy on ambulation using the Timed 25-Foot Walk (T25FW) and defining as ‘responders’ those patients who walked faster in two of three post-baseline T25FW assessments compared to baseline. The Authors found that the percentage of T25FW responders was higher in the NTZ group than in the placebo group (24% versus 12%, respectively) [38]. Similar results were obtained by a larger study of 548 SPMS and highly disabled 358 RRMS showing that patients treated for up to 30 months with NTZ alone, or in combination with intramuscular interferon beta-1a (IFNβ-1a) more frequently showed improvement in T25FW than patients who received placebo or IFNβ-1a alone [40]. The ASCEND study failed to demonstrate a significant reduction of disability progression (primary outcome) measured by a multicomponent model including the EDSS, 9-Hole Peg Test (9HPT), and the T25FW [24]. On the other hand, a significant 44% reduction in the relative risk of confirmed upper-limb disability progression as measured by the 9HPT was observed during NTZ treatment. In comparison with our study, in the ASCEND population a greater proportion of patients (about 52%) in the NTZ-treated arm progressed according to the multicomponent model at week 108. This could be explained by the older age and the higher level of disability level (median EDSS 6.0) of the ASCEND cohort compared to ours.

More interestingly, our study found that higher EDSS at treatment onset and longer SPMS duration were risk factors for higher rates of disability accrual in terms of PIRA, even adjusted for the presence of

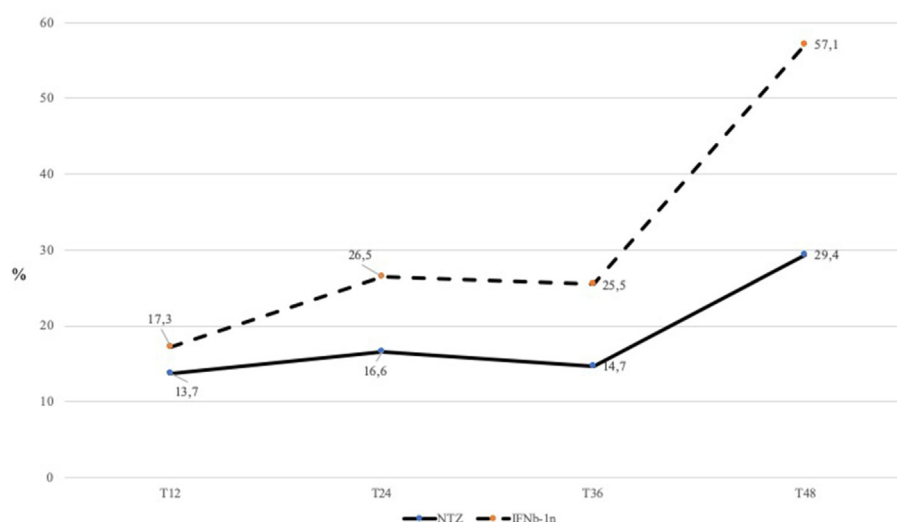


Fig. 2. Percentage of patients developing disability progression independent from relapse activity (PIRA) during NTZ or IFN-1b treatment (after propensity matching). IFN-1b: interferon beta 1b; NTZ: natalizumab.

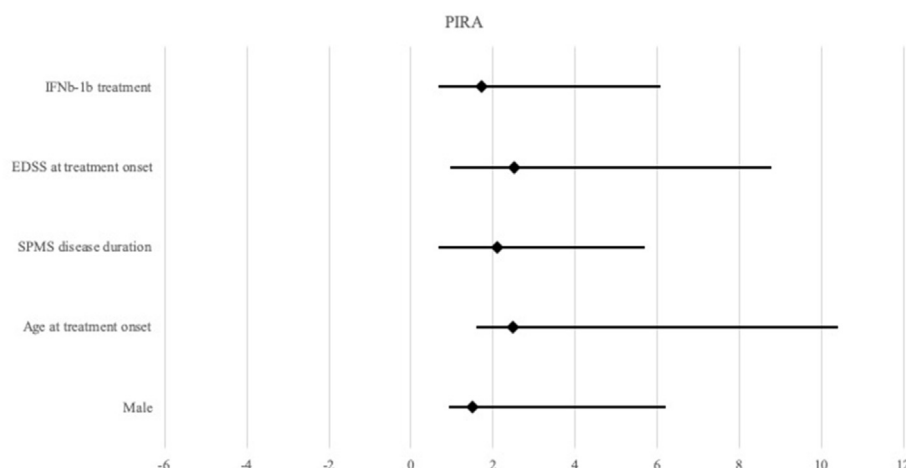


Fig. 3. Multivariate analysis^a of developing disability progression independent from relapse activity (PIRA) during NTZ or IFNb-1b treatment. NTZ: natalizumab; PIRA: progression independent from relapse activity. a data are reported as Hazard ratio (HR) and 25% confidence interval.

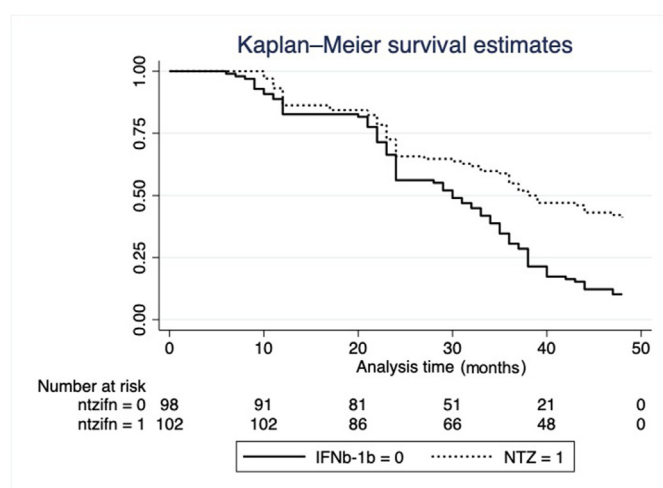


Fig. 4. Kaplan Meier curves for the time of reaching PIRA during NTZ and IFNb-1b. IFNb-1b: interferon beta 1b; NTZ: natalizumab, PIRA: progression independent from relapse activity.

disease activity. These results were in line with Novartis-Oxford multiple sclerosis (NO.MS) data pool, showing that pre-existing disability represents the main risk factor for further disability accumulation [32]. Moreover, patients treated with IFNb-1b were 1.64 times more to likely to develop PIRA compared to NTZ. Notably, NTZ is also known to significantly reduce intrathecal inflammatory responses resulting in reduced risk of developing new brain/spine lesions and brain atrophy, as well as to modulate microglial function, CNS macrophage infiltration, microglial and/or blood-derived macrophage activation, that are potentially involved in the pathophysiology of SPMS [23,41,42].

According to our analysis, the presence of active SPMS disease seems to not impact the disability outcomes. This is apparently in contrast with a recent multicenter study comparing the clinical effectiveness of high- and low-efficacy treatments in patients with recently active and inactive SPMS. In this study, second-line therapies were more efficacious than those with lower efficacy in reducing relapses in patients with active SPMS [43]. However, in both active and inactive SPMS, no evidence for a difference in the risk of disability progression between high- and low-efficacy therapies was observed [43].

Our study has several limits. The retrospective design of our study may have limited the statistical power of our results. As a consequence, a possible selection bias may be due to continuous treatment for at least 48

months resulting in a post-treatment assignment that could have selected the small subset for whom treatments were effective. Since efficacy and safety are the main driving forces behind switching/interrupting DMTs, this bias could be minimized considering that the cohort is composed by SPMS patients in whom relapses rarely occur and that primary endpoint of this study was the risk of disability progression in terms of PIRA and CEW. Moreover, in the light of the lack of approved drugs for the treatments of SPMS in the period of the data extraction, DMTs may have been maintained even in case of disability worsening as no other options were available at the time. Second, the use of EDSS evaluations as clinical endpoint may underestimate the disability progression in our cohort because of a low event rate and fluctuation in scores. For instance, EDSS not adequately assesses disease progression driven by other functional domains, mainly cognition and fatigue [44]. Presumably, a more thorough assessment of disease progression in SPMS patients should take into account more insidious manifestations of MS disability (i.e. depression, sexual problems, bladder/bowel dysfunctions, etc.). In addition, MRI data were collected with non-standardized MRI protocols and different scanners in the clinical routine, limiting the consistency and reliability of our results. Similarly, we did not evaluate brain volume and/or brain atrophy patterns. Nevertheless, the present multicenter, real-world study prospectively collected data over 48 months, with a longer follow-up compared to previous studies. Finally, it cannot be ruled out that the presence of comorbidities may have influenced the disability outcomes, as it is associated with greater disability and relapse risk [45]. Future longitudinal studies may overcome these issues.

In conclusion, findings from our study indicated that the efficacy of NTZ may exert long-term beneficial effects on early SPMS patients, with more favorable disability outcomes compared to IFNb-1b, thus suggesting its possible use in this group of patients.

Author contributions

CGC and FP contributed to study concept and design, to analysis and interpretation of data and to drafting of the manuscript. UA, MPA, RB, AB, SB, VBM, PC, EC, AC, SC, GDL, ADS, MF, AG, CG, FG, GL, DM, GTM, GM, LM, DP, IP, PR, MR, GS, CS, RT, ST, MT, MV, MZ and VL contributed to acquisition of data, to analysis and interpretation of data, to study supervision and approved the final manuscript.

Declaration of competing interest

CGC has received grants to attend scientific congresses or speaker honoraria from Biogen, Merck-Serono, Novartis, Roche, Sanofi/Genzyme, Teva.

UA reports no disclosures relevant to the manuscript.

MPA has received grants to attend scientific congresses or speaker honoraria from Biogen, Merck-Serono, Novartis, Roche, Sanofi/Genzyme, Teva.

RB reports no disclosures relevant to the manuscript.

AB has received grants to attend scientific congresses or speaker honoraria from Biogen, Merck-Serono, Novartis, Roche, Sanofi/Genzyme, Teva.

SB served as speaker and/or advisory board fee, and/or travel grant from Novartis, Teva, Sanofi-Genzyme, Roche, Biogen-Idec, Merck-Serono.

VBM received fees for consultancies or public speaking from Merck, Novartis, Biogen, Roche, Genzyme and Biogen.

PC has served as an advisory board member for Almirall, Biogen, Merck-Serono, Sanofi-Genzyme, Roche, Teva; she has received grants to attend scientific congresses or speaker honoraria from Biogen, Merck-Serono, Novartis, Roche, Sanofi/Genzyme, Teva.

EC reports no disclosures relevant to the manuscript.

AC reports no disclosures relevant to the manuscript.

SC has received grants to attend scientific congresses or speaker honoraria from Biogen, Merck-Serono, Novartis, Roche, Sanofi/Genzyme, Teva.

GDL reports no disclosures relevant to the manuscript.

ADS reports no disclosures relevant to the manuscript.

MF is Editor-in-Chief of the Journal of Neurology; received compensation for consulting services and/or speaking activities from Biogen Idec, Merck-Serono, Novartis, Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Merck-Serono, Novartis, Teva Pharmaceutical Industries, Roche, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and ARISLA (Fondazione Italiana di Ricerca per la SLA).

AG reports no disclosures relevant to the manuscript.

CG reports no disclosures relevant to the manuscript.

FG received grants to attend scientific congresses or speaker honoraria from Biogen, Merck-Serono, Novartis, Roche, Sanofi/Genzyme, Teva.

GL reports no disclosures relevant to the manuscript.

DM reports no disclosures relevant to the manuscript.

GTM has received grants to attend scientific congresses or speaker honoraria from Biogen, Merck-Serono, Novartis, Roche, Sanofi/Genzyme, Teva.

GAM has served as an advisory board member and received speaker honoraria, congress, travel and accommodation expense compensations from Merck, Teva, Mylan, Bayer, Novartis, Roche, Almirall, Biogen and Sanofi Genzyme.

LM reports no disclosures relevant to the manuscript.

DP has received grants to attend scientific congresses or speaker honoraria from Biogen, Merck-Serono, Novartis, Roche, Sanofi/Genzyme, Teva.

IP reports no disclosures relevant to the manuscript.

PR reports no disclosures relevant to the manuscript.

MR received travel grants and fees for consulting and public speaking from Almirall, Biogen, Genzyme-Sanofi, Merck Serono, Mylan and Novartis.

GS has received grants to attend scientific congresses or speaker honoraria from Biogen, Merck-Serono, Novartis, Roche, Sanofi/Genzyme, Teva.

CS has received grants to attend scientific congresses or speaker honoraria from Biogen, Merck-Serono, Novartis, Roche, Sanofi/Genzyme, Teva.

RT reports no disclosures relevant to the manuscript.

ST reports no disclosures relevant to the manuscript.

MT has received grants to attend scientific congresses or speaker honoraria from Biogen, Merck-Serono, Novartis, Roche, Sanofi/Genzyme, Teva.

MV reports no disclosures relevant to the manuscript.

VL reports no disclosures relevant to the manuscript.

MZ has received grants to attend scientific congresses or speaker honoraria from Biogen, Merck-Serono, Novartis, Roche, Sanofi/Genzyme, Teva.

FP has received honoraria for speaking activities by Almirall, Bayer Schering, Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Genzyme, and TEVA; he also served as advisory board member the following companies: Bayer Schering, Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Genzyme, and TEVA; he was also funded by Pfizer and FISM for epidemiological studies; he received grants for congress participation from Almirall, Bayer Shering, Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Genzyme, and TEVA.

Acknowledgments

Carlo Avolio, Roberto Balgera, Paola Banfi, Paolo Bellantonio, Placido Bramanti, Lorenzo Capone, Guido Cavalletti, Luca Chiveri, Raffaella Clerici, Marinella Clerico, Francesco Corea, Vincenzo Dattola, Francesca De Robertis, Giancarlo Di Battista, Simonetta Galgani, Maurizia Gatto, Maria Grazia Grasso, Matilde Inglese, Lorenzo Lo Russo, Francesco Ottavio Logullo, Renato Mantegazza, Alessandra Protti, Monica Rezzonico, Mariaros Rottoli, Marco Salvetti, Elio Scarpini, Leonardo Sinisi, Maddalena Sparaco, Daniele Spitaleri, Tiziana Tassinari, Simone Tonietti, Paola Valentino, Franco Valzania, Simonetta Venturi.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neurot.2024.e00363>.

References

- [1] Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sorensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* 2014;83(3):278–86.
- [2] Milo R, Kahana E. Multiple sclerosis: geoeidemiology, genetics and the environment. *Autoimmun Rev* 2010;9(5):A387–94.
- [3] Weinshenker BG. The natural history of multiple sclerosis: update 1998. *Semin Neurol* 1998;18(3):301–7.
- [4] Cree BAC, Arnold DL, Chataway J, Chitnis T, Fox RJ, Pozo Ramajo A, et al. Secondary progressive multiple sclerosis: new insights. *Neurology* 2021;97(8):378–88.
- [5] Lublin FD, Coetzee T, Cohen JA, Marrie RA, Thompson AJ. International Advisory Committee on Clinical Trials in MS. The 2013 clinical course descriptors for multiple sclerosis: a clarification. *Neurology* 2020;94(24):1088–92.
- [6] Lorscheider J, Buzzard K, Jokubaitis V, Spelman T, Havrdova E, Horakova D, et al. Defining secondary progressive multiple sclerosis. *Brain* 2016;139(Pt 9):2395–405.
- [7] Iaffaldano P, Lucisano G, Guerra T, Patti F, Onofri M, Brescia Morra V, et al. Towards a validated definition of the clinical transition to secondary progressive multiple sclerosis: a study from the Italian MS Register. *Mult Scler* 2022;13524585221114007.
- [8] Kappos L, Bar-Or A, Cree BAC, Fox RJ, Giovannoni G, Gold R, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet* 2018;391(10127):1263–73.
- [9] EF U. Interferon b-1b (Betaseron) treatment of secondary progressive forms of multiple sclerosis. Clinical review of the June 28, 2000 amendment to supplemental BLA 98-0737-STN103471: Chiron Corp. FDA US Food and Drug Administration; 2001. <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsAreDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm088275pdf2010>. 2000.
- [10] La Mantia L, Vacchi L, Rovaris M, Di Pietrantonj C, Ebers G, Fredrikson S, et al. Interferon beta for secondary progressive multiple sclerosis: a systematic review. *J Neurol Neurosurg Psychiatry* 2013;84(4):420–6.
- [11] Correale J, Marrodan M, Ysraelit MC. Mechanisms of neurodegeneration and axonal dysfunction in progressive multiple sclerosis. *Biomedicines* 2019;7(1).
- [12] Carotenuto A, Signoriello E, Lanzillo R, Vaia Y, Moccia M, Bonavita S, et al. Unraveling diagnostic uncertainty in transition phase from relapsing-remitting to secondary progressive multiple sclerosis. *Mult Scler Relat Disord* 2020;43:102211.
- [13] Hughes J, Jokubaitis V, Lugaresi A, Hupperts R, Izquierdo G, Prat A, et al. Association of inflammation and disability accrual in patients with progressive-onset multiple sclerosis. *JAMA Neurol* 2018;75(11):1407–15.
- [14] Khoy K, Mariotte D, Defer G, Petit G, Toutirais O, Le Mauff B. Natalizumab in multiple sclerosis treatment: from biological effects to immune monitoring. *Front Immunol* 2020;11:549842.
- [15] Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006;354(9):899–910.

- [16] Lublin FD, Cutter G, Giovannoni G, Pace A, Campbell NR, Belachew S. Natalizumab reduces relapse clinical severity and improves relapse recovery in MS. *Mult Scler Relat Disord* 2014;3(6):705–11.
- [17] Bigaut K, Fabacher T, Kremer L, Ongagna JC, Kwiatkowski A, Sellal F, et al. Long-term effect of natalizumab in patients with RRMS: TYSTEN cohort. *Mult Scler* 2021; 27(5):729–41.
- [18] Harrer A, Tumani H, Niendorf S, Lauda F, Geis C, Weishaupt A, et al. Cerebrospinal fluid parameters of B cell-related activity in patients with active disease during natalizumab therapy. *Mult Scler* 2013;19(9):1209–12.
- [19] Khademi M, Bornsen L, Rafatnia F, Andersson M, Brundin L, Piehl F, et al. The effects of natalizumab on inflammatory mediators in multiple sclerosis: prospects for treatment-sensitive biomarkers. *Eur J Neurol* 2009;16(4):528–36.
- [20] Sellebjerg F, Bornsen L, Khademi M, Krakauer M, Olsson T, Frederiksen JL, et al. Increased cerebrospinal fluid concentrations of the chemokine CXCL13 in active MS. *Neurology* 2009;73(23):2003–10.
- [21] Aloisi F, Columba-Cabezas S, Franciotta D, Rosicarelli B, Magliozzi R, Reynolds R, et al. Lymphoid chemokines in chronic neuroinflammation. *J Neuroimmunol* 2008; 198(1–2):106–12.
- [22] Khademi M, Kockum I, Andersson ML, Iacobaeus E, Brundin L, Sellebjerg F, et al. Cerebrospinal fluid CXCL13 in multiple sclerosis: a suggestive prognostic marker for the disease course. *Mult Scler* 2011;17(3):335–43.
- [23] Romme Christensen J, Ratzner R, Bornsen L, Lyksborg M, Garde E, Dyrby TB, et al. Natalizumab in progressive MS: results of an open-label, phase 2A, proof-of-concept trial. *Neurology* 2014;82(17):1499–507.
- [24] Kapoor R, Ho PR, Campbell N, Chang I, Deykin A, Forrestal F, et al. Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension. *Lancet Neurol* 2018;17(5):405–15.
- [25] Trojano M, Bergamaschi R, Amato MP, Comi G, Ghezzi A, Lepore V, et al. The Italian multiple sclerosis register. *Neurol Sci* 2019;40(1):155–65.
- [26] Trojano M, Butzkueven H, Kappos L, Wiendl H, Spelman T, Pellegrini F, et al. Natalizumab treatment shows low cumulative probabilities of confirmed disability worsening to EDSS milestones in the long-term setting. *Mult Scler Relat Disord* 2018;24:11–9.
- [27] Kalincik T, Cutter G, Spelman T, Jokubaitis V, Havrdova E, Horakova D, et al. Defining reliable disability outcomes in multiple sclerosis. *Brain* 2015;138(Pt 11): 3287–98.
- [28] Kappos L, Wolinsky JS, Giovannoni G, Arnold DL, Wang Q, Bernasconi C, et al. Contribution of relapse-independent progression vs relapse-associated worsening to overall confirmed disability accumulation in typical relapsing multiple sclerosis in a pooled analysis of 2 randomized clinical trials. *JAMA Neurol* 2020; 77(9):1132–40.
- [29] McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001;50(1): 121–7.
- [30] Faissner S, Gold R. Progressive multiple sclerosis: latest therapeutic developments and future directions. *Ther Adv Neurol Disord* 2019;12:1756286419878323.
- [31] StataCorp. Stata statistical software: release 17. College Station, TX: StataCorp LLC; 2021.
- [32] Lublin FD, Haring DA, Ganjgahi H, Ocampo A, Hatami F, Cuklina J, et al. How patients with multiple sclerosis acquire disability. *Brain* 2022;145(9):3147–61.
- [33] Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European Study Group on interferon beta-1b in secondary progressive MS. *Lancet* 1998;352(9139):1491–7.
- [34] Panitch H, Miller A, Paty D, Weinshenker B. North American Study Group on Interferon beta-1b in Secondary Progressive MS. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. *Neurology* 2004;63(10): 1788–95.
- [35] Kappos L, Polman C, Pozzilli C, Thompson A, Beckmann K, Dahlke F, et al. Final analysis of the European multicenter trial on IFNbeta-1b in secondary-progressive MS. *Neurology* 2001;57(11):1969–75.
- [36] Kuhle J, Hardmeier M, Disanto G, Gugleta K, Ecsedi M, Lienert C, et al. A 10-year follow-up of the European multicenter trial of interferon beta-1b in secondary-progressive multiple sclerosis. *Mult Scler* 2016;22(4):533–43.
- [37] Miller DH, Khan OA, Sheremata WA, Blumhardt LD, Rice GP, Libonati MA, et al. A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2003;348(1):15–23.
- [38] Cadavid D, Tang Y, O'Neill G. [Responsiveness of the Expanded Disability Status Scale (EDSS) to disease progression and therapeutic intervention in progressive forms of multiple sclerosis]. *Rev Neurol* 2010;51(6):321–9.
- [39] Woodworth JDP, Fox E, Lucas N, Plavina T. Comparative pharmacokinetics and pharmacodynamics of subcutaneous and intravenous administration of natalizumab [abstract P529]. *Mult Scler* 2013;19:216–7.
- [40] Cadavid D, Jurgensen S, Lee S. Impact of natalizumab on ambulatory improvement in secondary progressive and disabled relapsing-remitting multiple sclerosis. *PLoS One* 2013;8(1):e53297.
- [41] Bornsen L, Christensen JR, Ratzner R, Oturai AB, Sorensen PS, Sondergaard HB, et al. Effect of natalizumab on circulating CD4+ T-cells in multiple sclerosis. *PLoS One* 2012;7(11):e47578.
- [42] de Andres C, Teijeiro R, Alonso B, Sanchez-Madrid F, Martinez ML, Guzman de Villoria J, et al. Long-term decrease in VLA-4 expression and functional impairment of dendritic cells during natalizumab therapy in patients with multiple sclerosis. *PLoS One* 2012;7(4):e34103.
- [43] Roos I, Leray E, Casey R, Horakova D, Havrdova E, Izquierdo G, et al. Effects of high- and low-efficacy therapy in secondary progressive multiple sclerosis. *Neurology* 2021;97(9):e869–80.
- [44] Uitdehaag BMJ. Disability outcome measures in phase III clinical trials in multiple sclerosis. *CNS Drugs* 2018;32(6):543–58.
- [45] Tettey P, Siejka D, Simpson Jr S, Taylor B, Blizzard L, Ponsonby AL, et al. Frequency of comorbidities and their association with clinical disability and relapse in multiple sclerosis. *Neuroepidemiology* 2016;46(2):106–13.