MSJ Experimental Translational Clinical

Original Research Paper

Onset of secondary progressive multiple sclerosis is not influenced by current relapsing multiple sclerosis therapies

Multiple Sclerosis Journal—Experimental, Translational and Clinical

April-June 2018, 1–12

DOI: 10.1177/2055217318783347

Francisco Coret*, Francisco C Pérez-Miralles, Francisco Gascón, Carmen Alcalá, Arantxa Navarré, Ana Bernad, Isabel Boscá, Matilde Escutia, Sara Gil-Perotin and Bonaventura Casanova

Abstract

Background: Disease-modifying therapies are thought to reduce the conversion rate to secondary progressive multiple sclerosis.

Objective: To explore the rate, chronology, and contributing factors of conversion to the progressive phase in treated relapsing–remitting multiple sclerosis patients.

Methods: Our study included 204 patients treated for relapsing–remitting multiple sclerosis between 1995 and 2002, prospectively followed to date. Kaplan–Meier analysis was applied to estimate the time until secondary progressive multiple sclerosis conversion, and multivariate survival analysis with a Cox regression model was used to analyse prognostic factors.

Results: Relapsing–remitting multiple sclerosis patients were continuously treated for 13 years (SD 4.5); 36.3% converted to secondary progressive multiple sclerosis at a mean age of 42.6 years (SD 10.6), a mean time of 8.2 years (SD 5.2) and an estimated mean time of 17.2 years (range 17.1–18.1). A multifocal relapse, age older than 34 years at disease onset and treatment failure independently predicted conversion to secondary progressive multiple sclerosis but did not influence the time to reach an Expanded Disability Status Scale of 6.0.

Conclusions: The favourable influence of disease-modifying therapies on long-term disability in relapsing–remitting multiple sclerosis is well established. However, the time to progression onset and the subsequent clinical course in treated patients seem similar to those previously reported in natural history studies. More studies are needed to clarify the effect of disease-modifying therapies once the progressive phase has been reached.

Keywords: Multiple sclerosis, disease-modifying therapies, secondary progressive multiple sclerosis, natural history, relapsing–remitting multiple sclerosis, interferons

Date received: 6 November 2017; Revised received 19 April 2018; accepted: 10 May 2018

Introduction

Multiple sclerosis (MS), a chronic disease with an unpredictable course, is recognised as a main cause of disability among young adults in developing countries.[1] Analyses of the natural history of the disease have shown that conversion from relapsing–remitting multiple sclerosis (RRMS) to secondary progressive multiple sclerosis (SPMS) is a critical event, both because it implies the inexorable progression of disability[2–4] and because available treatments have no efficacy in terms of modifying the course of the disease at this stage.[5–7]

Recent studies of RRMS with long-term follow-up have demonstrated that disease-modifying therapies (DMTs) reduce the proportion of patients who progress to SPMS compared to the proportion of untreated patients who progress.[5–7] Jokubaitis et al. reported that 38.7% of patients reached an

Correspondence to:
Bonaventura Casanova, Neuroimmunology Unit, Hospital Universitari i Politècnic La Fe, Avda. Fernando Abril Martorell, 102, 46026 València, Spain.
casanova.bonaventura@gmail.com

Francisco Coret*, Neuroimmunology Unit, Hospital Clínic de València, Spain

Francisco C Pérez-Miralles, Neuroimmunology Unit, Hospital Universitari i Politècnic La Fe, Spain

Francisco Gascón, Neuroimmunology Unit, Hospital Clínic de València, Spain

Carmen Alcalá, Neuroimmunology Unit, Hospital Universitari i Politècnic La Fe, Spain

Arantxa Navarré, **Ana Bernad**, Neuroimmunology Unit, Hospital Clínic de València, Spain

Isabel Boscá, **Matilde Escutia**, **Sara Gil-Perotin**, **Bonaventura Casanova**, Neuroimmunology Unit, Hospital Universitari i Politècnic La Fe, Spain

*Deceased

Expanded Disability Status Scale (EDSS) score of 4.0 after 10 years of treatment (±12 months);[5] Cree et al. reported that 10.1% of RRMS patients transitioned to SPMS after 9.9 years of follow-up since the first symptom (range 8.6–10.2);[6] and Rio et al. reported that 77 patients (31%) with RRMS had converted to SPMS after a mean follow-up of 12 years (range 2–17.3).[7] By contrast, other studies have failed to show an effect of first-line DMTs on SPMS conversion.[8,9]

Our work extends the observational period under treatment with DMTs to 18 years from the onset of RRMS, making it the longest observational study published on the subject to date. The aim of this study is to explore whether DMTs and/or clinical characteristics influence the rate of conversion to SPMS and the subsequent neurological decline leading to disability.[10]

Methods

Inclusion of patients

This is a retrospective study of prospectively collected data obtained from the Grup d'Investigació i Tractament de l'Esclerosi Múltiple/Group for Research and Treatment of Multiple Sclerosis (GITEM) Registry of MS patients. This registry, authorised by the health department of Valencia (Spain), contains recorded data from all the patients in the MS units of the Hospital Universitari i Politècnic La Fe and the Hospital Clínic Universitari since 1994. The GITEM registry is located on a server belonging to the health department of the Generalitat Valenciana in the Clinic University Hospital of València (Spain). The main data collected were as follows: demographic characteristics at baseline, EDSS at each scheduled visit, dates of relapses and functional systems affected, starting and ending dates of treatment, reason for treatment change, magnetic resonance imaging data and cerebrospinal fluid characteristics.

Patients who experienced a first episode suggestive of a demyelinating process between January 1994 and January 2002 were included in the study. The last date considered for analysis was 30 November 2016, except for patients lost to follow-up, for whom the last visit recorded in the database was considered the last visit.

MS diagnosis

The initial clinical syndromes were classified as focal (including optic neuritis, sensory symptoms of indeterminate origin and motor symptoms of indeterminate origin) or multifocal (including incomplete myelitis, brainstem syndrome and polyregional syndromes). The diagnosis of clinically definite multiple sclerosis (CDMS) was made according to Poser's criteria.[11] A relapse was defined as the onset of a new symptom or worsening of a preexisting symptom in an episode that lasts more than 24 hours and is not explained by fever or physical stress. The sole appearance or exacerbation of urinary symptoms, without any other neurological signs or symptoms, was not considered as a relapse.[12,13] Patients without a second relapse (clinically isolated syndrome) or with a progressive disease course at onset (primary progressive or progressive relapsing multiple sclerosis) were excluded. Patients diagnosed after the implementation of the McDonald criteria were not included in this study because of the resulting inherent change in clinical practice including diagnosis of CDMS and, therefore, initiation of treatment.[14,15]

Decisions on initiation and choice of therapy

Treatment with first-line DMTs (interferon beta or glatiramer acetate) was initiated when patients had experienced at least one relapse in the previous year or two relapses within the previous 3 years. Patients were switched to non-specific immunosuppressants (mitoxantrone or cyclophosphamide) or selective second-line DMTs (natalizumab or fingolimod) when treatment failure criteria were met. Treatment failure was defined as the occurrence of two or more relapses within a year despite correct treatment with first-line agents for at least 6 months. We use this definition because the criteria to begin treatment include one or more relapses in the previous year; consequently, to have two relapses in a year of treatment was considered a sign that the treatment was ineffective.[16]

Adverse effects were also a cause of treatment switch to a better tolerated drug (within first or second-line therapies). The use of second-line DMTs started when these drugs were available in our country. Natalizumab was approved on 26 September 2006, and fingolimod was approved on 13 April 2011.

Follow-up

Patients were monitored at scheduled visits every 3–6 months because all patients on DMTs must undergo regular analysis to monitor cell count, liver enzymes and thyroid hormones in the case of interferon beta treatment, according to the risk plan established by the health authority of our country

(all data on file). The attending physician recorded the EDSS score, the presence of relapses, side effects, and/or treatment discontinuation. SPMS was confirmed when patients with a previous EDSS score of 3.0 or greater experienced a 6-month worsening to EDSS 4.0 or greater without evidence of relapse.[17,18]

Times from disease onset to EDSS 3.0 and 6.0, as well as time from SPMS conversion to EDSS 6.0, were extracted from recorded data. The Multiple Sclerosis Severity Score (MSSS) was retrospectively calculated for the time at which treatment began (mean 4.3 years from onset) and for the last visit. Individual values were obtained from the intersection of the column corresponding to EDSS and the row corresponding to the number of years from the first MS event, which corrects EDSS for MS duration, in order to allow comparisons between an individual's disability and the distribution of scores in cases having equivalent disease duration in a European reference population of 9892 MS patients, as shown in Figure 3 in Roxburgh et al.[19]

Statistics

The software programs SPSS Statistics and GraphPad Prism were used for analysis. Survival analysis was used to generate Kaplan–Meier estimates of the time to reach EDSS 3.0, conversion to SPMS, time to EDSS 6.0 and the time interval between SPMS diagnosis and EDSS 6.0.

The hazard ratio (HR) of each potentially informative variable was obtained by Cox proportional hazard regression analysis after the patients were stratified by initial clinical syndromes, grouped age at disease onset and grouped time to reach an EDSS score of 3.0. The grouped variables were obtained by calculating the mean and the terciles. Gender, age at disease onset, time from first to second relapse, time from disease onset to the initiation of treatment, treatment duration, time from treatment initiation to treatment failure and time to reach an EDSS score of 3.0 or greater were included as covariates with possible predictive value. A second analysis was performed in order to explore the impact of left-censored cases on the final results (patients with an EDSS of 4.0 or higher as a result of the first relapse).

Handling patient loss. Deaths related to MS (EDSS 10.0) were defined as those due to a direct complication of MS or its treatment. Accordingly, suicides, accidental falling with cranial trauma and fracture of both femurs occurred in a patient, and unrelated concurrent diseases were recorded with the EDSS at the last visit, and this score was therefore used for calculations.[20] The last available EDSS score and visit date were considered in cases of discontinuation during follow-up. In the case of patient withdrawal, the date of the last dose of treatment and cause of withdrawal were recorded and used to calculate the time of effective treatment.

Bibliography/literature search strategy and selection criteria

Material for bibliographic comparison was selected by a PubMed search with the following terms: (a) 'natural history multiple sclerosis' and (b) 'long term treatment multiple sclerosis' and 'natural history', published before 1989. In both searches, we selected publications that reported follow-up periods of at least 11 years in relapsing MS patients. Long-term studies associated with clinical trials were excluded because of the potential bias caused by the high number of patients lost to follow-up.

Results

Study population

Among a total of 1709 patients included in the registry by 30 November 2016, 277 (16.2%) were diagnosed with clinically isolated syndrome between January 1994 and January 2002; among those, 225 (81.2%) developed CDMS with time (see Supplementary Tables 1–4), and of those who met the criteria for initiation of DMTs, 204 (90.6%) started treatment (Figure 1). The mean follow-up time from the onset of MS (first demyelinating event suggestive of MS) in the study group was 18.1 years (standard deviation (SD) 2.9). One hundred and eighty-four patients (90.2%) remained on the prescribed treatment at the last visit, with discontinuation in 18 patients for the following reasons: personal reasons ($n = 6$); side effects ($n = 5$), including three cases of 'flu-like syndrome and two cases of cutaneous necrosis; desire for pregnancy ($n = 4$); treatment inefficacy ($n = 2$) as determined by a neurologist; and change in diagnosis to neuromyelitis optica ($n = 1$). Patients who discontinued treatment were older than patients who continued therapy (35 vs. 29.7 years, $P = 0.03$), but no other significant differences were found between them.

During follow-up, there were 12 deaths (75% women); the mean age at death was 52.3 years,

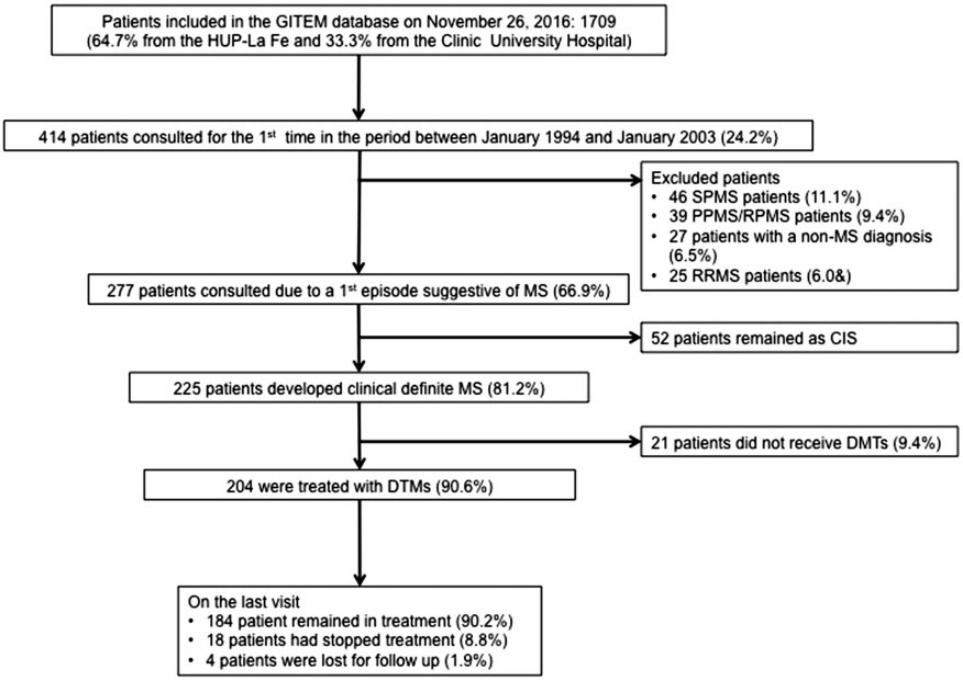

Figure 1. Flow chart of the patients included and reasons to exclude from the study.
SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; RPMS: relapsing progressive multiple sclerosis; CIS: clinically isolated syndrome; DMTs: diseases-modifying therapies.

with a range of 35–80 years. In six cases (2.2%), deaths were directly attributed to MS or to MS treatment, including four patients with aspiration pneumonia, one with pulmonary embolism and one with mitoxantrone-related promyelocytic leukaemia. Non-MS-related causes included suicide ($n = 2$), malignant neoplasms (cervical cancer and multiple myeloma), subarachnoid haemorrhage ($n = 1$) and myocardial infarction ($n = 1$).

Four patients (three women and one man) were lost to follow-up. The mean time under observation in these cases was 13 years (SD 2.7). The characteristics of these patients did not differ from those of the study group in general: age at first relapse was 30.2 years (SD 12.2) and mean EDSS at the last observation was 3.7 (SD 2.1). Three of them moved to another region/country, and one of them stopped his scheduled visits and could not be contacted. The last data on file were registered for patients lost to follow-up.

Twelve neurologists participated in data collection. The vast majority of visits were done by FC and BC; FCPM, CA, IB and FG also contributed to the scheduled visits; and some visits were done by ADV, AN, AP, CV, LL, and MJM.

Demographic and clinical data of our cohort

Two hundred and four patients were treated for a mean time of 12 years (SD 4.5); see Table 1. The mean time to initiation of DMTs from the first demyelinating event suggestive of MS was 4.8 years (SD 3.6), with DMTs beginning at a mean age of 33.6 years (SD 12.8). Eighty-eight patients (43.1%) were switched to second-line therapies because of treatment failure, and 29 patients (14.2%) were switched from a first-line therapy to another first-line treatment (in all cases, patients were switched from interferon beta to glatiramer acetate): 17 because of 'flu-like syndrome (58.6%), 11 because of dermatological events (37.9%) and one (3.4%) because a meningioma was diagnosed; see Table 2.

Results of the Kaplan–Meier survival analysis

For the entire survival analysis, MS onset was defined as the first event suggestive of a demyelinating process. One hundred and nine patients (53.4%) reached an EDSS of 3.0 in an estimated mean time of 14.1 years; 74 patients (36.3%) converted to SPMS in a mean time of 8 years (estimated mean time from Kaplan–Meier analysis 17.1 years); and 40 patients had an EDSS score of 6.0 (19.0%) in an estimated mean time of 19.9 years (Figure 2).

Table 1. Clinic and demographic characteristics of the two cohorts of patients studied: the cohort of the University Hospital La Fe (HUPLF) and the University Clinic Hospital (UCH) from València.

	Total series (n=204)	HUPLF cohort (n=163)	UCH cohort (n=41)
Gender			
Men (n, %)	57 (27.9)	50 (30.7)	7 (17.1)
Women (n, %)	147 (72.1)	113 (76.9)	34 (82.9)
Age at onset (mean, SD)	***30.3 (9.7)***	***30.4 (9.5)***	***29.6 (10.8)***
<24 years (n, %)	70 (34.3)	54 (33.1)	16 (39.0)
25–34 years (n, %)	74 (36.3)	61 (37.4)	13 (31.7)
>34 years (n, %)	60 (29.4)	48 (29.4)	12 (29.3)
MS duration (mean, SD)	***18.1 (2.9)***	***17.9 (3.0)***	***18.7 (2.4)***
Clinical syndrome at first relapse			
Monofocal syndromes	99 (48.6)	74 (45,4)	25 (61.0)
Optic neuritis	*34 (16.7)*	27 (16.6)	*7 (17.1)*
Indeterminate nonofocal symptoms	*65 (31.9)*	*47 (28.9)*	*18 (43.9)*
Multifocal syndromes	105 (51.4)	89 (54.6)	16 (39.0)
Myelitis	*47 (23)*	*43 (26.4)*	*4 (9.8)*
Brain-stem syndrome	*46 (22.5)*	*37 (22.7)*	*9 (22.0)*
Polyregional	*12 (5.9)*	*9 (5.5)*	*3 (7.3)*
Patients with 2nd relapses at time (n, %)			
<12 month	59 (28.9)	45 (27.6)	14 (34.1)
Between 12 and 27 month	71 (34.8)	52 (31.99	19 (46.3)
>27 months	74 (36.3)	66 (40.5)	8 (19.5)
Time to 2nd relapses (mean, DS)	*31.4 (34.9)*	*33.0 (33.1)*	*25.0 (41.2)*
Treatment disposition (n, %)			
One first-line DMTs	87 (42.6)	68 (41.7)	19 (46.3)
Two first-line DMTs	29 (14.2)	25 (15.3)	4 (9.8)
Second-line DMT	88 (43.1)	70 (42.9)	18 (43.9)
Disability evolution (mean, SD)			
MSSS (Multiple Sclerosis Severity Score)			
MSSS at the beginning of treatment	4.3 (2.5)	4.2 (2.6)	4.7 (2.0)
MSSS at the end of follow-up	3.1 (2.7)	3.0 (2.6)	3.4 (2.8)
Last MSSS in patients remaining RRMS (n=130)	*1.4 (.9)*	*1.4 (1.0)*	*1.4 (.7)*
Last MSSS in patients converted to SPMS (n=74)	*5.9 (2.4)*	*5.9 (2.4)*	*5.9 (2.5)*
EDSS (Expanded Disability Status Scale)			
Basal EDSS	1.6 (1.0)	1.5 (1.0)	1.6 (1.0)
EDSS at the beginning of treatment	2.4 (1.3)	2.3 (1.4)	2.6 (1.1)
EDSS at year 5	2.5 (1.5)	2.4 (1.6)	2.6 (1.2)
Last EDSS	3.5 (2.3)	3.4 (2.2)	3.9 (2.3)
Last EDSS in patients remaining as RRMS (n=130)	*2.1 (.8)*	*2.1 (.9)*	*2.3 (.6)*
Last EDSS in patients converted to SPMS (n=74)	*6.0 (1.8)*	*6.0 (1.8)*	*6.0 (2.2)*
Patients that reached an EDSS of 3.0 (n, %)	109 (53.4)	85 (52.1)	24 (58.5)
Time to EDSS 3 (mean, DS)	7.1 (4.2)	7.3 (5.6)	6.4 (4.2)
Patients that reached an EDSS of 6.0 (n, %)	40 (19.6)	30 (18.4)	10 (24.4)
Time to EDSS 6 (mean, DS)	9.3 (5.1)	9.3 (5.1)	10.0 (5.6)
Patients converted to SPMS (n, %)	***74 (36.3)***	***56 (34.4)***	***18 (43.9)***
Mean age (SD) at conversion	42.6 (10.8)	42.7 (11.0)	42.2 (10.3)
Time to SPMS (mean, DS)	8.2 (5.4)	8.3 (5.8)	8.0 (4.2)
Deceased patients (n, %)	***12 (5.9)***	***10 (6.1)***	***2 (4.9)***

RRMS: relapsing–remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

Table 2. Characteristics of patients according the last treatment received.

	First-line treatment	Second-line treatment	*P* value
Treatment (n, %)	116 (56.9)	88 (43.1)	
One first-line DMT all the time	87 (42.6)	–	
Two first-line DMTs	29 (14.2)	–	
Second-line treatments			
Mitoxantrone		36 (40.9)	
Natalizumab		18 (20.5)	
Cyclophosphamide		10 (11.4)	
Azathioprine		9 (10.2)	
Fingolimod		6 (6.8)	
Autologous stem cell transplant		5 (5.7)	
Rituximab		4 (4.5)	
Characteristics of patients grouped according to the last treatment received			
Women (*n*, %)	84 (70.7)	63 (71.6)	ns
Age at onset (mean, SD)	31.3 (10.2)	28.9 (9.0)	ns
Time between 1st and 2nd relapse (months)	37.3 (38.2)	23.5 (28.6)	0.005
Time to treatment (years)	5.0 (3.5)	4.1 (3.2)	0.05
Time to treatment failure (years)	–	4.2 (3.5)	–
Time under treatment (years)	13.0 (4.5)	11.9 (5.0)	ns
Patients converted to SPMS (*n*, %)	27 (36.5)	47 (63.5)	<0.0001
Patients who began 2nd-line as SPMS (*n*, %)	–	52 (59.0)	
Current EDSS (mean, SD)	2.8 (2.1)	4.7 (2.5)	<0.0001

DMTs: disease-modifying therapies; ns: not significant.

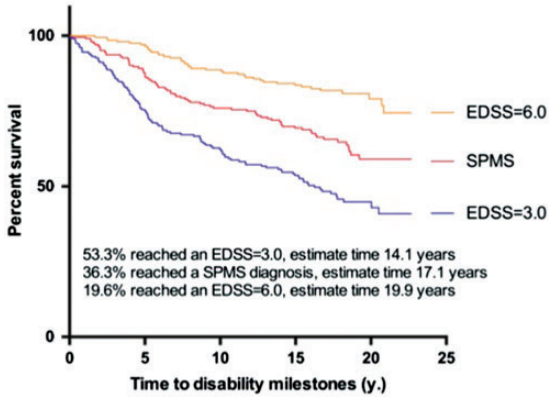

Figure 2. Kaplan–Meier survival analysis to reaching disability milestones of 3.0, 6.0 and the diagnosis of secondary progressive multiple sclerosis (SPMS).
EDSS: Expanded Disability Status Scale.

The variables associated with reaching an EDSS of 3.0 were older age and a multifocal syndrome at onset. Neither the time to a second relapse nor the use of second-line DMTs was predictive (Table 3). The predictive variables for reaching a diagnosis of SPMS were older age and/or multifocal syndrome at onset; time to reach an EDSS of 3.0, and the switch to second-line therapies due to treatment failure. These variables were also predictive of reaching an of EDSS 6.0 (Table 3).

Among 109 patients who had reached an EDSS score of 3.0, 40 (36.7%) worsened to EDSS 6.0 after a mean time of 13.4 years. Both older age at first attack and shorter latency to reach EDSS 3.0 predicted faster progression to EDSS 6.0. Among 74 patients who reached EDSS 3.0 and converted to SPMS, 40 (54%) reached EDSS 6.0 after a mean time of 9 years. In SPMS patients, no variables were found to be associated with progression to EDSS 6.0 (Table 4).

Fifty-two patients initiated second-line DMTs after SPMS conversion (64.7%) and progressed to EDSS 6.0 after an estimated mean time of 12 years from the first MS event, whereas among RRMS patients who switched to second-line therapies, only 9.5% reached EDSS 6.0, similar to the rate among those who continued with first-line therapies, with an estimated time to EDSS 6.0 of 21 years. The estimated median ages for the groups to reach EDSS 6.0 were 54 years and 61 years, respectively.

Table 3. Kaplan–Meier survival analysis to the time to reach an EDSS of 3.0, a SPMS diagnosis and EDSS of 6.0.

	Time to reach an EDSS of 3.0				Time to SPMS			Time to reach an EDSS of 6.0		
	N	Events (*n*, %)	Censored (*n*, %)	Mean (95% CI)	Events (*n*, %)	Censored (*n*, %)	Mean (95% CI)	Events (*n*, %)	Censored (*n*, %)	Mean (95% CI)
Total series	**204**	**109 (53.4)**	**95 (46.6)**	**14.1 (12.0–16.3)**	**74 (34.7)**	**130 (63.3)**	**17.2 (16.1–18.1)**	**40 (19)**	**164 (81.0)**	**19.9 (19.1–20.9)**
Gender										
Women	147	79 (53.7)	68 (46.3)	14.0 (12.6–15.4)	56 (38.1)	91 (61.9)	16.9 (15.6–18.1)	28 (19.0)	119 (81.0)	19.9 (19.0–20.9)
Men	57	30 (52.6)	27 (47.4)	14.1 (12.0–16.3)	18 (31–6)	39 (68.4)	17.6 (15.8–19.4)	12 (21.1)	45 (78.9)	19.4 (18.0–20.7)
Clinical syndrome at onset[a]										
Monofocal syndromes	99	42 (42.4)	57 (57.6)	16.5 (15.0–18.0)	24 (24.2)	75 (75.8)	19.4 (18.2–20.6)	9 (9.1)	90 (90.9)	21.4 (20.6–22.2)
Multifocal syndromes	105	67 (63.8)	38 (36.2)	11.7 (10.0–13.3)	50 (47.6)	55 (52.4)	14.9 (13.3–16.5)	31 (29.5)	174 (70.5)	18.2 (17.0–19.5)
Age at the beginning[b]										
<25 years old	70	26 (37.1)	44 (62.9)	16.5 (14.6–18.4)	19 (27.1)	51 (72.9)	18.9 (17.4–20.4)	11 (17.7)	59 (84.3)	20.4 (19.2–21.6)
25–34 years old	74	34 (45.9)	40 (54.1)	15.8 813.9–17.6)	19 (23.7)	55 (74.3)	19.0 (17.5–20.5)	6 (8.1)	68 (91.9)	21.2 (20.2–22.2)
>34 years old	60	49 (81.7)[2]	11 (18.3)[2]	9.0 (7.2–10.9)	36 (60.0)	24 (40.0)	12.5 (10.5–14.6)	23 (38.3)	37 (61.7)	16.9 (15.2–18.6)
Time to second relapse										
<12 months	59	34 (57.6)	25 (42.4)	12.4 (13.6–14.6)	24 (40.7)	35 (59.3)	16.3 (14.4–18.2)	11 (18.6)	48 (81.4)	19.5 (18.0–20.9)
12–27 months	71	38 (54.5)	33 (46.5)	14.0 (11.9–16.0)	27 (38.0)	44 (62.0)	16.7 (14.8–18.6)	17 (23.9)	54 (76.1)	19.2 (17.7–20.7)
> 27 months	74	37 (50.0)	37 (50.0)	15.3 (13.6–17.1)	23 (31.1)	51 (68.9)	17.9 (16.2–19.5)	12 (16.2)	62 (83.8)	20.0 (19.1–21.4)
Time to EDSS 3.0 (109)[c]										
<7.2 years	66	na	na	na	55 (85.3)	11 (16.7)	8.4 (6.8–10.1)	36 (54.5)	30 (45.5)	14.4 (12.7–16.2)
>7.2 years	43	na	na	na	19 (44.2)	24 (55.8)	18.3 (17.1–19.6)	4 (9.3)	39 (90.7)	21.3 (20.7–22.0)
Treatment[d]										
One first-line DMT	87	32 (36.8)	55 (63.2)	17.0 (15.4–18.6)	20 (33)	67 (77.0)	19.1 (17.8–20.5)	8 (9.2)	79 (90.8)	21.3 (20.6–22.1)
Two first-line DMTs	29	12 (41.4)	27 (58.6)	16.7 (13.9–19.4)	7 (24.1)	22 (75.9)	19.7 (17.6–21.7)	3 (10.3)	26 (89.7)	21.4 (20.1–22.8)
Second-line DMTs	88	65 (73.9)	23 (26.1)	10.1 (8.4–11.8)	47 (53.4)	41 (46.6)	14.1 (12.4–15.8)	29 (43.0)	59 (67.0)	17.5 (16.0–19.0)

[a]Multifocal syndromes reached an EDSS=3.0 (P=0.0002), EDSS=6.0 (P=0.00016) and SPMS (P=0.00015) earlier.
[b]Patients older than 34 years reached an EDSS=3.0 (P=0.003), a SPMS diagnosis (P<0.0001); an EDSS=6.0 (P<0.001) earlier.
[c]Patients that reached an EDSS 3.0 earlier, reached a diagnosis of SPMS and an EDSS=6.0 earlier (P<0.0001 in both cases).
[d]Patients switched to second-line DMT reached earlier an EDSS 3.0 (P<0.0001 front one first-line DMT; and 0.001 front two first-line DMTs), and SPMS (P<0.00002 front one first-line DMT; and P=0.005 front two first-line DMTs); and an EDSS=6.0 (P<0.0001 front one first-line DMTs; and P=0.016 front two first-line DMTs).
SPMS: secondary progressive multiple sclerosis; na: not applicable. DMTs: disease-modifying therapies.

Table 4. Time (in years) to reaching an EDSS 6.0 in patients that reached an EDSS 3.0, and in SPMS patients.

	Time from EDSS 3.0 to EDSS 0f 6.0					Time from SPMS to EDSS 0f 6.0				
	N	Events (*n*, %)	Censored (*n*, %)	Mean (95% CI)	Median (95% CI)	*N*	Events (*n*, %)	Censored (*n*, %)	Mean (95% CI)	Median (95% CI)
Total series	**109**	**40 (36.7)**	**69 (63.3)**	**13.4 (11.7–15.2)**	**15.5 (11.8–19.2)**	**74**	**40 (45.9)**	**34 (54.1)**	**9.0 (6.9–11.1)**	**5.1 (3.0–7.3)**
Gender										
Women	79	28 (35.4)	51 (64.6)	13.9 (11.9–15.9)	–	56	28 (50.0)	28 (50.0)	9.9 (7.4–12.4)	6.3 (1.8–10.8)
Men	30	12 (40.0)	18 (60.0)	12.4 (9.2 (15.6)	15.5 (7.9–23.1)	18	12 (66.7)	6 (33.3)	5.7 (3.4–7.9)	4.7 (3.7–5.7)
Clinical syndrome at onset										
Monofocal syndromes	42	9 (21.4)	33 (78.6)	13.3 (11.4–15.1)	–	24	9 (37.5)	15 (62.5)	9.0 (6.3–11.6)	8.9
Multifocal syndromes	67	31 (46.3)	36 (53.7)	12.2 (10.0–14.3)	11.2 (4.7–17.7)	50	31 (62.0)	19 (38.0)	7.9 (5.6–10.3)	4.9 (3.6–6.3)
Age at the beginning										
<25 years old	26	11 (42.3)	15 (57.7)	13.2 (10.1–16.4)	19.5	19	11 (57.9)	8 (42.1)	6.7 (4.1–9.4)	4.3 (1.8–6.9)
25–34 years old	34	6 (7.6)	28 (82.4)	14.0 (11.8–16.1)	–	19	6 (31.6)	13 (68.4)	9.9 (5.9–13.8)	
>34 years old[a]	49	23 (46.9)	26 (53.1)	11.5 (9.0–14.1)	8.2 (3.6–12.8)	36	23 (63.9)	23 (36.1)	8.1 (5.4–10.8)	5.1 (0.7–9.6)
Time to second relapse										
< 12 months	34	11 (33.4)	23 (67.6)	14.7 (12.1 (17.3)	19.5	24	11 (45.8)	13 (54.2)	8.7 (5.6–11.7)	5.0 (3.2–6.9)
12–27 months	38	17 (44.7)	21 (55.3)	10.9 (8.2–13.5)	–	27	17 (63.0)	10 (37.0)	6.6 (3.9–9.4)	4.9 (1.3–8.6)
>27 months	37	12 (32.4)	25 (67.6)	13.3 (10.0–16.6)	11.6	23	12 (52.2)	11 (47.8)	10.0 (6.2–13.7)	6.3 (0.01–12.7)
Time to EDSS 3.0 (109)										
<7.2 years[b]	66	36 (54.5)	30 (45.5)	12.1 (10.1–14.1)	13.2 (6.0–20.3)	55	36 (65.5)	19 (34.5)	8.3 (6.1–10.5)	4.9 (3.6–6.3)
>7.2 years	43	4 (9.3)	39 (90.7)	12.2 (10.7–13.8)	–	19	4 (21.1)	15 (78.9)	9.4 (6.9–11.9)	
Treatment										
One DMTs	32	8 (25.0)	24 (75.0)	14.2 (11.5 (16.9)	15.5 812.6–18.4)	20	8 (40.0)	12 (60.0)	11.2 (7.3–15.0)	8.9 (5.3–12.5)
Two DMTS	12	3 (25.0)	9 (75.0)	15.2 (9.9–20.6)	–	7	3 (42.9)	4 (57.1)	9.0 (1.0–17.0)	2,6 (.01–5.3)
Second line therapies	65	29 (44.6)	36 (55.4)	12.0 (10.9–14.1)	19.5	47	29 (61.7)	18 (38.3)	7.2 (5.2–9.2)	4.3 (2.3–6.4)

[a]Time to reach an EDSS 6.0 was shorter in patients >34 years old.
[b]The number of patients who reached the EDSS 6.0 was lower if EDSS=3.0 was reached after the year 7.
SPMS: secondary progressive multiple sclerosis; DMTS: disease-modifying therapies.

Results of the Cox proportional multivariate regression analysis

Older age and multifocal syndromes, either at disease onset or at treatment failure, independently predicted shorter times to EDSS 3.0, EDSS 6.0 and/or SPMS conversion. Male gender seemed to act as an independent protective factor, but only when predictive variables were analysed for the switch to SPMS (Table 5). The results from the Cox multivariate regression analysis for the time to reach EDSS 6.0 in 191 patients (93.6%), in whom the baseline EDSS after the first relapse was lower than 3.5 (left censoring to the Kaplan–Meier analysis), did not differ from the results obtained among treated patients overall (Table 5).

Discussion

In this 18-year study of the effect of DMTs on RRMS in real-world conditions, we have observed a decrease in the number of patients who reached an EDSS of 3.0 and, consequently, a lower rate of conversion to SPMS. In addition, we found that the number of patients who reached an EDSS of 6.0 was reduced. Overall, we observed that once SPMS was reached, the time to reach an EDSS of 6.0 was similar to the time reported in natural history studies.

We observed a reduced proportion of patients who reached an EDSS score of 3.0 after the observational period compared to previous series with comparable follow-up times.[2,3] The largest difference was detected 14 years after disease onset (53.4% vs. 81%). Along the same lines, we also found that fewer patients reached an EDSS score of 6.0 in this study than in the longest natural history studies.[2–4,21–23] However, the times to reach an EDSS score of 6.0 from disease onset (19 years) and once progression started (9 years) resembled those reported in the natural history studies.[2,23]

At the beginning of treatment, patients were in the 5th decile (4.37) of the MSSS distribution.[19,24] After 18 years of follow-up, the MSSS decreased to the 4th decile (3.37). As the MSSS would be expected to remain in the 5th decile if no treatment were given (4.27), this decrease is the net effect of treatment. By contrast, the MSSS at year 18 of patients who converted to SPMS was between the 6th and 7th decile (5.98); and in the 130 patients who remained as RRMS, the MSSS at the last observation decreased from the 5th decile to the 2nd decile (1.47); these findings are similar to those reported by Enzinger et al.[25]

We are aware of the difficulty of comparing our results with those of natural history studies due to the different proportions of treated patients, the different durations of follow-up and the different methodology. However, the conversion to SPMS in 36.3% of patients after 18 years of follow-up implies a relevant reduction compared with the 58% of patients who developed SPMS in the same follow-up time in the British Columbia series,[2] or the 66.3% in the series from London, Ontario, although in the latter series we must take into account the long period of observation (28 years).[3]

When the switch to progression occurred, the estimated mean time to SPMS conversion was comparable to that reported in most of the natural history studies published to date.[2,23] Zeydan and Kantarci have suggested that underlying mechanisms of progression not influenced by DMT exist from the beginning of the disease and become evident when patients are in their forties, explaining this phenomenon.[26,27]

According the criteria to treat MS patients with DMTs in our country, these therapies should be withdrawn when an EDSS higher than 6.5 is reached. In clinical practice, this criterion is very difficult to implement because continuous inflammatory activity despite an SPMS course has been demonstrated, and as a consequence, patients can still benefit from DMTs.[28] Along the same lines, the new classification of progressive MS forms into active and inactive could help with therapeutic decisions.[29]

Multivariate analysis of potential associated variables revealed that older age and multifocal syndrome at onset, as well as treatment failure, were predictive factors for SPMS conversion and progression to EDSS 3. Older patients have a four-fold risk of reaching the secondary progressive phase, as has been observed in natural history studies, which points to the independence of the progressive phase from the inflammatory in treated patients. We did not find any clinical or demographic factor that could influence the rate of progression to an EDSS score of 6.0 once a secondary progressive course had been confirmed (9 years from SPMS), in line with natural history studies.[30] The fact that treatment was withdrawn in 18 older patients could bias the study towards more inflammatory forms, but the multivariate survival analysis using a Cox regression model showed that age and treatment failure were independent of the evolution to SPMS; for

Table 5. Cox regression multivariate analysis to the time to reach an EDSS = 3.0, a SPMS diagnosis and EDSS = 6.0; and in the 191 patients with an EDSS lower than 3.5 after the first relapse. (Left bias to Kaplan–Meier analysis).

	N	HR (95% CI) to EDSS 3.0	HR (95% CI) to SPMS	HR (95% CI) to EDSS=6
Gender				
Women	147	1	1	1
Men	57	0.7 (0.5–1.2)	0.5 (0.3–0.9)	0.6 (0.3–1.4)
Clinical syndrome at onset				
Monofocal syndromes[a]	99	1	1	1
Multifocal syndromes[b]	105	1.4 (0.9–2.2)	1.9 (1.1–3.2)	2.9 (1.3–6.2)
Age at the beginning				
<25 years old1	70	1	1	1
25–34 years old	74	1.4 (0.8–2.5)	1.0 (0.5–1.9)	0.5 (0.1–1.4)
>34 years old	60	4.0 (2.4–6.6)	3.6 (2.0–6.6)	3.1 (1.4–6.9)
Time to second relapse				
>27 months	74	1	1	1
12–27 months	71	1.3 (0.8–2.1)	1.3 (0.7–2.2)	1.6 (0.7–3.3)
<12 months	59	1.5 (0.9–2.5)	1.5 (0.8–2.7)	1.2 (0.5–2.6)
Treatment failure				
No TF	116			
TF criteria	88	3.1 (2.0–4.6)	3.1 (1.9–5.2)	4.6 (2.2–9.6)
Gender				
Women	138	1	1	1
Men	53	0.7 (0.5–1.2)	0.5 (0.2–1.0)	0.6 (0.3–1.5)
Clinical syndrome at onset				
Monofocal syndromes[a]	98	1	1	1
Multifocal syndromes[b]	93	1.3 (0.8–2.0)	1.6 (0.9–2.8)	2.2 (1.0–5.1)
Age at the beginning				
<25 years old[1]	68	1	1	1
25–34 years old	72	1.5 (0.8–2.6)	1.0 (0.5–2.1)	0.4 (0.1–1.4)
>34 years old	51	4.0 (2.3–6.8)	3.6 (1.9–7.0)	3.3 (1.4–7.8)
Time to second relapse				
>27 months	69	1	1	1
12–27 months	66	1.3 (0.8–2.2)	1.4 (0.7–2.7)	2.2 (0.8–5.7)
<12 months	56	1.7 (1.0–2.8)	1.7 (0.9–3.3)	1.8 (0.6–5.1)
Treatment failure				
No TF	111	1		
TF criteria	80	3.3 (2.1–5.1)	3.4 (1.9–5.9)	4.8 (2.0–11.5)

1: Reference.
[a]Monofocal syndromes include: optic neuritis, sensitive monofocal symptom of indeterminate origin and motor monofocal symptom of indeterminate origin.
[b]Multifocal syndromes include: myelitis, brainstem syndrome and polyregional syndrome.
HR: hazard ratio; CI: confidential interval; SPSS: secondary progressive multiple sclerosis; TF: treatment failure.

this reason, we believe that this bias had minimal weight, if any.

The rate of treatment failure was 43.1% after a mean time of 5 years. Other studies report 28% in 3 years,[31] 34% after 5 years[32] and 27% or 43.8% in 3 years.[33,34] Thus our results are based on a high proportion of patients on second-line DMTs. Among those patients with treatment failure who initiated second-line agents after confirmation of SPMS, 66% of them progressed to an EDSS score of 6.0, showing an analogous profile to patients

described in the natural history studies. Similar findings have been reported in recent series.[28]

The number of MS-related deaths in this study was in line with the results of published studies (2.2%), and no MS deaths related to therapy emerged after prolonged exposure to treatments, except for one case of acute leukaemia related to mitoxantrone.[35]

The importance of data from registers and observational studies is paramount for clinical research.[36] The main limitations of our work are the absence of a control group, the relatively low number of patients and the inter-rater scoring variability in the EDSS measurements over the years. Possible bias in real-word studies arises from the variability of time to begin DMTs and changes between them, as well as from the definitions of treatment failure and progression. In our study, these biases were minimised by the strict definition of treatment failure and by our definition of SPMS, which was decided after the publication of our previous work based on the North-American interferon beta 1b trial on SPMS and the SPECTRIMS trial.[17,18,37]

In conclusion, we consider it likely that long-term treatment with DMTs might reduce the number of patients who will develop SPMS. However, in patients who do convert to SPMS, time to conversion, age of transition and subsequent cumulative disability are not influenced by current therapies.

Author contribution

FC and BC were the attending physicians during the first 10 years and for the final visits at the close of the study; they also designed the database, the treatment protocol, the criteria of therapeutic failure, and the follow-up study. FCPM and FG participated in the design of the statistical analysis. CA, AN and SGP carried out the data collection. AB and ME participated in the data entry. BC, FCPM, CA and SGP have written and revised the manuscript. FG, AN and IB reviewed and discussed the manuscript.

Acknowledgements

The authors would like to thank all patients who participated during these 18 years and all the staff involved in caring for and attending to MS patients: Dr Mara Andreu (1998–2004), Dr Alma Bueno (1998–2004), Inmaculada Cal (2010–2014), Encarnación García (1995–2001), Dr Ana De Vera (1998–2001), Dr Lamberto Landete (1995–1998), Dr María José Magraner (2007–2011), Nuria Mas (2014–2015), Beatriz Muria (2013–2016), Dr Ana Pascual (2004–2008), Dr María Simó (2004–2012) and Dr Caridad Valero (1997–2000).

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was funded by Health Institute Carlos III #PS13/00663 (BC) and #CM12/00014 (SGP).

Supplementary material

Supplementary material is available for this article online.

ORCID iD

Sara Gil-Perotin http://orcid.org/0000-0003-3793-0116
Bonaventura Casanova http://orcid.org/0000-0003-3806-925X

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