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G. Edan, study concept and design, analysis and interpretation of data critical revision of manuscript for intellectual content

A. Kerbrat, study concept and design, analysis and interpretation of data, study supervision, critical revision of manuscript for intellectual content

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ABSTRACT

Background: Changes in relapse activity during secondary progressive MS (SPMS) need to be accurately characterized in order to identify patients who might benefit from continuing disease-modifying therapies.

Objective: To describe relapse occurrence in patients with SPMS during long-term follow up, and assess its impact on disability worsening.

Methods: This retrospective cohort study included 506 patients. We assessed the influence of relapses on time from SPMS onset to an Expanded Disability Status Scale score of 6 (EDSS 6), and on irreversible worsening of EDSS scores across different periods.

Results: The annualised relapse rate (ARR) decreased with patient's age (mean reduction of 43% per decade) and SPMS duration (mean reduction of 46% every 5 years). Post-progression relapses were associated with shorter time from SP phase onset to EDSS 6 (HR = 1.29, 95% CI [1.01, 1.64]). Relapse occurrence during the first 3 years and 3-5 years after SP onset was associated with an increased risk of irreversible EDSS worsening (OR = 3.12 [1.54, 6.31] and 2.04 [1.16, 3.58]). This association was no longer significant after 5 years.

Conclusion: The occurrence of relapses was a marker of short term disability progression during early SPMS, but did not have decisive impact in later SPMS.

INTRODUCTION

The shift from relapsing-remitting MS (RRMS) to secondary progressive MS (SPMS) is far from clearcut, and different subtypes of SPMS have recently been defined [1], to take account of persistent focal activity (active vs. nonactive SPMS) and disease progression (progressing vs. nonprogressing SPMS). It is important to identify these different stages of MS in clinical routine, as they respond differently to current therapeutic strategies. Thus, in patients with RRMS, disease-modifying therapies (DMTs) have consistently been shown to have a significant impact on the annualised relapse rate (ARR) and short-term disability progression [2], whereas during the SPMS phase, their impact remains uncertain in the absence of persistent relapse activity. Indeed, in four of five randomized placebo-controlled trials of interferon beta conducted in patients with SPMS [3–6], treatment was found to have no effect on disability progression scored on the Expanded Disability Status Scale (EDSS) [7], while the fifth study yielded conflicting results [8]. However, this fifth study had included younger patients, and had a higher percentage of patients with pre-study relapses than the other studies. The Expand study on the use of siponimod in patients with SPMS recently reported positive results on disability progression [9], but in the subgroup analyses, the treatment effect became less pronounced with increasing age and diminishing signs of disease activity. The benefit of monoclonal antibodies in older patients with no persistent inflammatory activity is similarly questionable [10,11].

Therefore, changes in relapse activity need to be accurately described, in order to better identify patients who might benefit from continuing DMTs during SPMS [12,13]. This is a critical issue, given the safety profile and the costs of the new DMTs. Although a number of natural history studies have investigated early relapses during the RR phase of the disease [14–21], few have provided descriptions of late relapses [22,23], and none have focused on patients with SPMS over a long period of regular follow up.

The aims of the present study were therefore to i) describe changes in relapse frequency in an SPMS population during long-term follow up with regular clinical examinations, ii) identify predictive factors for relapse persistence during SPMS, and iii) assess the impact of relapses on disability worsening, depending on the timing of their occurrence after SP phase onset.

METHODS

Database

All our patients were diagnosed according to Poser's classification [24]. They were identified through the Rennes MS clinic database, which uses European Database for Multiple Sclerosis (EDMUS) software [25] and was set up in January 1976. Since that date, all new cases of MS have been systematically registered in the database. Historical data (date of clinical onset, relapses, disability and treatment) were retrospectively obtained from records of the patients' first visit. Follow-up data were then prospectively collected. For the present study, data were extracted from the database on 1 March 2017. The database was approved by the French data protection authority (CNIL).

Patient selection

Patients were retrospectively selected according to three inclusion criteria. i) They had to have a diagnosis of SPMS, established by an MS specialist neurologist and defined as a history of gradual worsening, after an initial relapsing disease course, with or without acute exacerbations during the progressive course [1]. The date of transition to SPMS entered in the database was systematically checked in the patients' medical records. ii) The SPMS phenotype had to have lasted for at least 3 years, in order to have sufficient time to clearly assess the disease course. iii) Patients had to undergo regular follow up at the Rennes MS clinic. They were typically assessed once a year. We excluded patients who were only occasionally referred from other centres for an expert judgment (Figure 1).

Data collection

The following data were extracted from the Rennes EDMUS database: demographic data, relapses, DMTs and disability. The relapses occurring during the SP phase were systematically checked in the patients' medical records. A *relapse* was defined as new or worsening neurological symptoms attributable to MS, not associated with fever or infection, lasting at least 24 hours, and validated by an MS specialist neurologist. In most cases, an objective change on neurological examination was prospectively validated by the MS specialist neurologist during an unscheduled visit. However, in a minority of cases where patients had not requested an additional visit, a relapse may have been retrospectively diagnosed during a scheduled annual appointment, based on patient interview and potentially on a persistent change on neurological examination. For each relapse, the clinical description was reported, together with the occurrence of complete remission or not. Moreover, given the difficulty of identifying *true* relapses during SPMS, we systematically collected (when available) magnetic resonance imaging (MRI) data within 6 months of a relapse, and specified the presence of any new T2 lesions and gadolinium-enhancing lesions. Disability was scored at each visit by an MS specialist neurologist, using the EDSS. A score was deemed to be irreversible when it persisted for at least 1 year, and up to the last visit. In particular, we focused on the EDSS score at SPMS transition and 3, 5, 10 and 15 years later, and on EDSS 6. Disability worsening was defined as an increase in the EDSS score of at least 1 point if the baseline EDSS was 5.5 or less, or 0.5 point if the baseline EDSS was more than 5.5. For DMTs, we considered immunomodulators (glatiramer acetate, interferon, teriflunomide, dimethyl fumarate) and immunosuppressants (mitoxantrone, natalizumab, fingolimod, cyclophosphamide, azathioprine, methotrexate, alentuzumab) as DMTs.

Statistical analysis

Qualitative (expressed as number of patients (%)) and quantitative (expressed as mean with *SD*) variables were compared using appropriate statistical tests (chi2 test for qualitative variables, independent *t* test for means, Wilcoxon-Mann-Whitney for noncontinuous variables). ARRs (total number of relapses in a given period divided by the total number of person-years in that period) were computed for different time intervals (first 5 years after SP phase onset, 5-10 years, 10-15 years, and after 15 years) and according to each patient's age (below 30 years, 30-40 years, 40-50 years, 50-60 years, and after 60 years). This analyse was repeated after removing periods under treatment.

Time to first relapse, and to second relapse, during the SP phase was subjected to survival analysis. For patients who did not have a relapse, time to event was right-censored at the date of their last visit. Mean times and event probabilities for different time intervals were estimated using the Kaplan–Meier method. Multivariate Cox proportional hazard models were used to identify factors associated with time-to-event outcomes: sex, age at SP phase onset, disease duration at SP phase onset, disability at SP phase onset, and DMTs during SP phase. For DMTs, we deemed that patients who had been treated for less than 3 months were untreated. For this analysis, DMT was treated as a time-dependent variable. We also specifically studied the association between DMT duration and relapse occurrence. We considered four different durations: < 1 year, 1-3 years, 3-5 years, and > 5 years. We also focused on the first 5 years of the SP phase, considering two categories: treated for more or less than 3.4 years (median duration of treatment). For these analyses, DMT was not treated as a time-dependent variable. We also specifically studied the association between type of DMT (immunomodulator vs. immunosuppressant with or without immunomodulator) and relapse occurrence. Quantitative variables that did not respect the log-linearity assumption

were transformed into categorical variables. Results were expressed as hazard ratios (HRs) with 95% CIs.

The same analysis was conducted to explain time to EDSS 6, introducing the occurrence of at least one relapse during the SP phase but before EDSS 6 as an additional potential explanatory factor. This factor and the use of DMTs were considered as time-dependent variables. Patients who reached EDSS 6 before onset of progression were excluded for this analysis.

To look for a potential link between clinical disease activity and short-term disability progression, we divided the SP phase into four periods (first 3 years, 3-5 years, 5-10 years, and 10-15 years after SP phase onset). We then built a logistic regression model to identify factors associated with irreversible disability worsening for each period, which was independently analysed. Disability progression in each period was defined as an increase in the EDSS score of at least 1 point if the baseline EDSS was 5.5 or less, and 0.5 point if the baseline EDSS was more than 5.5.

Results were expressed as odds ratios (ORs) with 95% CIs. For each model, factors associated with dependent variables with p values < 0.20 in the univariate analysis were introduced in the multivariate analysis, and backward selection was then applied. P values below 0.05 for two-tailed tests were considered to be statistically significant. Statistical analyses were performed with SAS software (V. 9.4).

RESULTS

Population characteristics

A total of 506 patients were eligible for the present study. The characteristics of the SPMS population are set out in Table 1 and 2. Mean follow-up duration was 24.4 ± 10.2 years from MS onset (12 346 person-years) and 14.3 ± 7.3 years from SP phase onset (7 236 person-years). The mean number of neurological assessments per patient during the follow up was 1.4 ± 0.4 per year (no significant difference between RR and SP phases). The 506 patients included in the study were compared with the 562 patients who were excluded owing to lack of regular follow up (see Fig. 1). Their mean age at disease onset and their mean disease duration at SP onset were similar (29.3 ± 8.5 vs. 30.3 ± 9.0 years, $p = 0.053$, and 10.6 ± 7.2 vs. 11.1 ± 7.6, $p = 0.35$).

Description of relapses during SP phase (table 2)

We recorded 414 relapses during the SP phase and 2112 during the RR phase. Out of 506 patients, 177 (35.0%) experienced at least one relapse, 107 (21.1%) at least two relapses, and 59 (11.7%) at least three relapses during the SP phase. the cumulative probability of having at least one relapse within 5, 10 and 15 years of SP onset was 23.7%, 33.6% and 37.6% (Fig. 2A). After a first relapse, the likelihood of having a second relapse within the following 5 years was 56.5% (Fig. 2B). However, after 5 years without relapse, this figure fell to just 14.8% (Fig. 2C).

Relapse rate according to patient age and disease duration

First, the ARR decreased regularly with SPMS duration, with a mean reduction of 46% every 5 years (Fig. 3A). Similarly, the ARR decreased with patient's age during the SP phase, with a mean reduction of 43% every decade (Fig. 3B). Figure 3C shows the ARR, taking patient's

age at SP onset and patient's current age at relapse occurrence (i.e. disease duration) into account. Both factors influenced the ARR. For example, if a patient was currently aged 50-60 years and had just entered the SP phase (SP onset after 50 years in Fig. 3C), his or her ARR was about 0.07. However, if a patient of the same age had entered the SP phase 20 years earlier (SP onset at 30-40 years in Fig. 3C), his or her ARR was just 0.02.

The direction of findings did not differ when ARRs were calculated after removing the period of follow up spent on DMT, corresponding to 39.3% of total follow-up duration during SPMS (Supplementary Fig. 1).

Factors associated with relapse occurrence during SP phase

The results are detailed in Table 3. In the univariate analysis, the following factors were associated with relapse occurrence during the SP phase: i) shorter disease duration (p = 0.004); ii) younger age at SP onset (p = 0.0001); and iii) DMT (p = 0.03). In the multivariate analysis, the patient's age at SP onset was the only significant parameter (HR = 0.97, 95% CI [0.95, 0.98], p = 0.0001). DMT duration (< 1 year, 1-3 years, 3-5 years or > 5 years, and > or < 3.4 years during the first 5 years of the SP phase) was not associated with relapse occurrence. Treatment by immunomodulator rather than immunosuppressant was associated with relapse (HR = 1.83 [1.13; 2.97]).

Association between relapses and time from SP phase onset to EDSS 6

The results are detailed in Table 4. The median time from SP onset to EDSS 6 was 6.7 years. Relapse occurrence after SP onset was significantly associated with a shorter time from SP onset to EDSS 6 in the multivariate analysis (HR = 1.30, 95% CI [1.02, 1.66], p = 0.03). A higher EDSS score at SP phase onset and DMTs during the SP phase were also associated with a shorter time from SP phase onset to EDSS 6 (p < 0.0001 and p = 0.001).

Association between relapses and short-term disability worsening

For the purpose of this analysis, we divided the SP phase into four distinct time intervals: first 3 years after SP onset, 3-5 years, 5-10 years, and 10-15 years. We specifically tested the association between relapses and disability worsening for each of the time intervals. The results are set out in Table 5 (see Supplementary Tables 1-4 for details). Relapse occurrence was significantly associated with an EDSS score increase between SP onset and 3 years (OR = 3.12 [1.54, 6.31]) and between 3 and 5 years (OR = 2.04 [1.16, 3.58]). This association was no longer significant between 5 and 10 years (OR = 1.27 [0.7, 2.3]) and between 10 and 15 years (OR = 1.21 [0.45, 3.27]).

DISCUSSION

Frequency of relapses during SPMS

We reported the frequency of relapses in a large cohort of patients with SPMS undergoing long-term regular follow up (12 346 person-years, 1.4 neurological assessments per patient per year). We identified patient's age at SP onset as the main determinant of relapse occurrence, and to a lesser extent, time from SP phase onset. These results were in line with previous natural history [22, 26, 27], MRI [28] and pathological [29] studies. These observations also have practical implication. Relapse activity can be suppressed by the DMTs that are currently available. However, the impact of these therapies has not yet been clearly demonstrated in patients with SPMS who have no inflammatory activity [3–6, 8–11, 30]. Changes in relapse activity with patient age and disease duration is thus a key issue in clinical routine. For example, in our cohort, the ARR dropped below 0.05 after age 50 years or after 10 years of SPMS. Interestingly, a 5-year relapse-free period during the SP phase was associated with a low likelihood of having a relapse during the subsequent 5 years (14.8%), whereas after a first relapse, the likelihood of having a second relapse within the following 5 years increased to 56.5%. This observation could be an additional criterion for identifying

patients with a low or high risk of clinical inflammatory activity during the SP phase. Finally, in our study, we found higher relapse frequency than a previous study in SPMS [23] after age 55 years (12.8% vs. 4.8%) and after 5 years of SPMS (36.7% vs. 8.4%). This discrepancy can probably be attributed to the longer duration of follow up in our population.

Relapses and disability progression

Earlier natural history studies [31–33] had found no influence of relapses on disability worsening during the SP phase, but a more recent study [23] reported conflicting results. These studies are summarized in Table 6. Different outcomes and analyses were used in these studies, making it difficult to compare the results. However, the more recent study [23] used an analysis and outcome (time from SP onset to EDSS 6) similar to ours, as well as a similar number of patients, and reached the same conclusion (i.e. association between relapse occurrence during SPMS and time from SP phase onset to EDSS 6). Interestingly, our second analysis dividing the SP phase into four periods nuanced this result, and possibly provided an explanation for the earlier negative studies. More specifically, we only found a positive association for relapse occurrence and irreversible disability worsening during the first 5 years of SPMS, and not during the subsequent 10 years. Our interpretation of these results is that relapses occurring during the first years of SPMS still have a significant impact on disability worsening, whereas in the later stages of SPMS, the occurrence of relapses have a lower impact. Another degenerative process, independent of focal inflammation might become predominant [29].

Concerning the potential impact of treatment, in our study, DMTs for at least 3 months during SPMS were associated with a shorter time from SP onset to EDSS 6. Similarly, we found a positive association between relapse occurrence during the SP phase and DMTs for at least 3 months. This apparently *paradoxical* results probably reflect the fact that patients with

persistent relapses and more severe disease were more likely to be treated and is consistent with a previous study [23]. It also suggests that the patients with SPMS who had persistent relapses under treatment represented a particular subgroup of patients with a more severe disease course. However, we need to emphasise that our study was not designed to assess the impact of DMTs on relapses or disability worsening, and methodological issues prevent us from reaching any firm conclusions in this respect. The patients were treated with a wide variety of drugs, in different combinations and for varying durations, which prevented us from comparing different therapeutic strategies.

Limitations

First, pinpointing when SPMS starts is obviously difficult. In our study, we used the definition of the recently proposed classification of progressive MS [1]. SPMS was retrospectively diagnosed by MS specialist neurologists who followed the patients on a yearly basis and was based on a history of gradual worsening after an initial relapsing disease course. It should be noted that in our jurisdiction, diagnosis of SPMS does not deprive patients of access to DMTs, and so does not influence neurologists' clinical reports. Moreover, the SPMS phenotype had to have lasted for at least 3 years, in order to have sufficient time to clearly assess the disease course, and the date of the diagnosis was systematically reviewed in the patient's medical records. Another definition of SPMS using EDSS score criteria was recently proposed [34]. This definition required a minimum EDSS score of 4 and a minimum pyramidal functional score of 2. In our study, the EDSS score at SPMS diagnosis was lower than in the proposed definition (median EDSS score = 3), but was similar to other studies [15,23]. The MS specialist neurologists probably detected subtle forms of progression in our cohort before EDSS 4. Second, another limitation in our study might concern relapse diagnosis in SP phase: identifying relapses in a condition in which disability can vary from day to day and according to different processes is a challenge both for the neurologist and for

the patient. Thus, the frequency of relapse could have been underestimated in our study. On one hand, patients with SPMS probably consult less for minor or moderate neurological symptoms, and could forget to mention them at the yearly follow-up visit. On the other hand, relapses were assessed mostly on clinical grounds in our study, as MRI data were not systematically available. Thus, it could have been difficult for the neurologist to confirm a relapse, especially retrospectively, based on patient interview. To partly overcome this limitation, these critical data were systematically checked in the patients' medical records. Moreover, in order to emphasize a prospective collection of these data, we chose to exclude from our analysis 562 patients without regular follow up. When we compared patients who had been included in the study with those who had been excluded, we found that they had similar demographic characteristics. Third, a large proportion of our patients were treated, preventing us from reporting a true natural history of MS. However, the direction of our findings on the ARR did not differ when analyses were repeated after removing data collected under DMTs (supplementary Fig. 1). Fourth, the unequal changes between the EDSS steps [35] are a potential confounding factor. Patients with lower EDSS scores during early SPMS are more likely to progress than patients with higher EDSS scores. This point was illustrated in our study by the significant association between a lower EDSS score and an EDSS score increase in each period (Supplementary Fig. 1-4). From 4 onwards, the EDSS score relies mainly on lower limb function, with the other functions contributing less. Consequently, the effect of relapses on these functions later on in the disease is more difficult to evaluate.

Conclusion and perspectives

Despite these limitations, the present study yielded arguments in favour of a relationship between relapse occurrence during early SPMS and short-term disability worsening, but suggested that late relapses do not have a decisive impact on disability progression in SPMS. Moreover, it was the youngest patients with the most persistent focal activity who were the

most concerned. Thus, if the use of DMTs would appear to be more justified in younger patients with early SPMS, the continuation of DMTs in older patients with SPMS may result in adverse effects outweighing any possible benefits of the drugs. Overall, given the small effect of relapses on disability accumulation, the risk-benefit ratio of therapy should be carefully considered.

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Table 1: Baseline characteristics of the secondary progressive MS population

Characteristics	**SPMS population**
Number of patients (%)	506
Sex	
Women (%)	320 (63.2)
Follow up duration during SP phase in years (mean ± SD)	14.3 (7.3)
Disease progression	
Age at MS onset in years (mean ± *SD*)	29.8 ± 8.6
Age at SP onset in years (mean ± *SD*)	40.4 ± 8.6
Time to reach SPMS in years (mean ± *SD*)	10.6 ± 7.3
Treatment during SP phase	
Number of treated patients (%)	405 (80)
Treatment duration in years (mean ± *SD*)	5.3 ± 4
Percentage of time under treatment (mean ± *SD*)	39.3 ± 25.5
Type of treatment (no. patients, %)	

Immunomodulator	
Interferon beta 1A	103 (25.4)
Interferon beta 1B	126 (31.1)
Glatiramer acetate	102 (25.2)
Teriflunomide	5 (1.2)
Dimethyl fumarate	7 (1.7)
Immunosuppressant	
Azathioprine	79 (19.5)
Cyclophosphamide	68 (16.8)
Mitoxantrone	218 (53.8)
Methotrexate	151 (37.3)
Natalizumab	9 (2.2)
Fingolimod	15 (3.7)
Alemtuzumab	5 (1.2)

Table 2: Characteristics of the population according to relapse occurrence during follow up

Characteristics	**SPMS population**		
	SPMS patients with at least one relapse	SPMS patients without relapse	*p**
Number of patients (%)	177 (35.0)	329 (65.0)	
Sex			
Women (%)	111 (62.7)	209 (63.5)	0.90
Follow up duration during SP phase in years (mean ± SD)	13.8 (6.1)	14.5 (7.8)	0.30
Disease progression			
Age at MS onset in years (mean ± *SD*)	28.9 ± 7.9	30.2 ± 8.8	0.10
Age at SP onset in years (mean ± *SD*)	38.3 ± 8.2	41.6 ± 8.6	**< 0.001**
Time to reach SPMS in years (mean ± *SD*)	9.4 ± 6.2	11.3 ± 7.7	**0.004**
Treatment during SP phase			
Number of treated patients (%)	159 (89.8)	246 (74.8)	**0.04**

Treatment duration in years (mean ± *SD*)	5.8 ± 4	4.9 ± 4	**0.04**
Percentage of time under treatment (mean ± *SD*)	43.3 ± 24.4	36.6 ± 25.6	**0.01**
EDSS scores during SP phase			
At SP onset (median and quartiles)	3 (3, 4)	3 (3, 4)	0.77
At 5 years (median and quartiles)	5.5 (5.5, 6)	5.5 (5.5, 6)	0.35
At 10 years (median and quartiles)	6.5 (6.5, 7)	6 (6, 7)	0.83
At 20 years (median and quartiles)	7 (7, 8.5)	7 (7, 8)	0.26
Relapse phenotype (%)			
Motor	31.2		
Increased walking difficulties	18.2		
Sensory	13.3		
Brainstem/cerebellum	14.0		
Optic neuritis	6.5		
Multiple symptoms	13.3		
Others	3.6		
Relapse with incomplete recovery (%)	39.7		

Relapse with brain MRI scan within 6 month (%)	31.0		
MRI with contrast enhancement (%)	58.2		
MRI with increase in T2 lesion load without contrast enhancement (%)	12.1		

SPMS: secondary progressive multiple sclerosis; EDSS: Expanded Disability Status Scale.

**Independent* t *test for quantitative continuous data, Wilcoxon-Mann-Whitney for noncontinuous variables, chi-square test for qualitative data, significant at* $p < 0.05$.

Table 3: Factors associated with relapse occurrence during secondary progressive phase

	Study population (*N* = 506)	Patients with relapse(s) (*n* = 177)	Univariate analysis		Multivariate analysis	
			HR [95% CI]	*P*	HR [95% CI]	*P*
Sex						
female	320	111	1		Not included ***	
male	186	66	1.03 [0.76; 1.39]	0.86		
Age at SP phase onset*	506	177	0.97 [0.95; 0.98]	0.0001	0.97 [0.95, 0.98]	0.0001
Disease duration at SP phase onset*	506	177	0.97 [0.95; 0.99]	0.004	Not significant	
Disability at SP phase onset						
EDSS < 4	360	128	1	0.87	Not included***	
EDSS ≥ 4	144	49	1.03 [0.74; 1.43]			
DMTs during SP phase**						
No	74	12	1	0.03	Not significant	
Yes	432	165	1.43 [1.04; 1.98]			

* For 1 year.

** Time-dependent variable.

*** Factors associated with dependent variables with *p* values > 0.20 in the univariate analysis were not introduced in the multivariate analysis.

HR = hazard ratio; 95% CI = confidence interval at 95%; EDSS = Expanded Disability Status Scale; SP = secondary progressive; DMT = disease modifying therapy.

Table 4: Factors associated with shorter time from secondary progressive phase onset to EDSS 6

	Study population (*N* = 477)	Time from SP onset to EDSS 6	Patients reaching EDSS 6 (*n* = 391)	Univariate analysis HR [95% CI]	*p*	Multivariate analysis HR [95% CI]	*p*
Sex							
female	300	6.6	250	1			
male	177	7.2	141	0.85 [0.69, 1.05]	0.14	Not significant	
Age at SP phase onset							
< 30 years	56	6.0	51	1	0.41	Not included***	
30-40 years	174	6.9	146	0.78 [0.57 ; 1.08]			
40-50 years	179	7.0	144	0.74 [0.54, 1.03]			
50-60 years	63	6.8	46	0.71 [0.48, 1.06]			
≥ 60 years	5	5.6	4	0.96 [0.35, 2.67]			

Disease duration at SP phase onset							
< 6 years	150	7.0	128	1	0.056	Not significant	
6-10 years	115	6.1	99	1.19 [0.92, 1.55]			
10-15 years	111	6.7	90	0.99 [0.76, 1.30]			
≥ 15 years	101	7.5	74	0.78 [0.59, 1.04]			
Relapses during SP phase**							
No	352		291	1	0.003	1	0.03
Yes	125		100	1.43 [1.13, 1.81]		1.30 [1.02, 1.66]	
Disability at SP phase onset	475		391				
EDSS < 4	360	7.5	285	1		1	
EDSS ≥ 4	115	4.5	104	2.16 [1.72, 2.71]	<0.0001	2.17 [1.72, 2.72]	<0.0001
DMTs during SP phase**							
No	186		160	1	<0.0001	1	0.001
Yes	291		231	1.55 [1.25, 1.93]		1.45 [1.15, 1.81]	

** Time-dependent variables. Mean time from SP onset to EDSS 6 can't be estimated in this case

*** Factors associated with dependent variables with *p* values > 0.20 in the univariate analysis were not introduced in the multivariate analysis.

HR = hazard ratio; 95% CI = confidence interval at 95%; EDSS = Expanded Disability Status Scale; SP = secondary progressive; DMT = disease modifying therapy.

Table 5: Association between relapses and short-term disability progression during SPMS.

time intervals	**0-3 years (*n* = 479)**	**3-5 years (*n* = 458)**	**5-10 years (*n* = 347)**	**10-15 years (*n* = 208)**
Patients with at least one relapse (*n*)	82	62	69	21
Odds ratio [95% CI]	2.89 [1.44; 5.80] *	2.04 [1.16; 3.57] *	1.27 [0.7; 2.3]	1.21 [0.45; 3.27]
***R*²**	0.0321	0.0286	0.0018	0.0007

n: number of patients.

**** adjusted for disease duration and sex. Detailed results are provided in Supplementary Tables 1-4.***

Table 6: Summary of previous studies of the impact of relapses occurring during secondary progressive MS or after EDSS 3 on disability progression

Study and population	Number of patients with SPMS	Disability progression outcome	Analysis	Results
Confavreux et al., NEJM 2000 (Lyon, France)	483	Time from EDSS 4 to 6, 4 to 7, and 6 to 7	Comparison of SPMS patients with and without superimposed relapses	No difference in time from EDSS 4 to 6. Time from EDSS 4 to 7 and from 6 to 7 longer for patients with superimposed relapses
Tremlett et al., Neurology 2009 (British Columbia, Canada)	529	Time from PPO to EDSS 6	Study of influence of relapses occurring after PPO on time from PPO to EDSS 6 (survival analysis)	No influence of relapses occurring during SP phase
Leray et al., Brain 2010 (Rennes, France)	618	Time from EDSS 3 to 6	Study of influence of relapses occurring after EDSS 3 (patients who converted with PPO before EDSS 3 were excluded) on disability outcome (survival analysis)	No influence of relapses on time from EDSS 3 to 6
Paz Soldan et al., Neurology 2015 (Mayo Clinic, United	533	Time from PPO to EDSS 6	Study of influence of relapses occurring after PPO on time from PPO to	Reduced time to EDSS 6 associated with relapses

States)			EDSS 6 (survival analysis)	
Kremenchutzky et al., Brain 2006** (London, Ontario, Canada)	286	Time from PPO to EDSS 6, 8 and 10	Comparison between SAP and SP	No difference between groups
Scalfari et al., Brain 2010** (London, Ontario, Canada)	534	Time from PP0 to EDSS 6, 8 and 10	Study of influence of relapses occurring in RR phase on disability outcome (survival analysis)	More relapses occurring solely during first 2 years of RR phase were associated with less time from PPO to EDSS 6, 8 and 10

SP: secondary progressive; RR: relapsing remittent; SAP: single relapse before progression; PPO: progressive phase onset; EDSS: Expanded Disability Status Scale; SPMS: secondary progressive multiple sclerosis.

Patients with RRMS and SPMS were included

****** Relapses occurring during the SP phase were not clearly assessed in these studies.***

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Figure 1: Selection of patients from the Rennes MS clinic EDMUS database

EDMUS: European Database for Multiple Sclerosis; EDSS: Expanded Disability Status Scale; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis.

Figure 2: Relapse occurrence during secondary progressive MS phase: (A) Time from SPMS onset to first relapse (*n* = 506 patients), **(B)** Time from first relapse to second relapse (*n* = 177 patients), **(C)** Time from first 5 years without relapse during SPMS to subsequent relapse (*n* = 452 patients).

Figure 3: Annualized relapse rate according to patient's current age, disease duration and age at secondary progressive onset: (A) time after SP (secondary progressive) phase onset, (B) patient's current age, (C) patient's current age and patient's age at SP onset. The number of patients in each group is detailed in the table.

Annualised relapse rate = (relapse count/number of days indicated by each patient) x 365.25.

Figure e-1: Annualized relapse rate according to patient's current age after removing time spent on disease modifying treatments

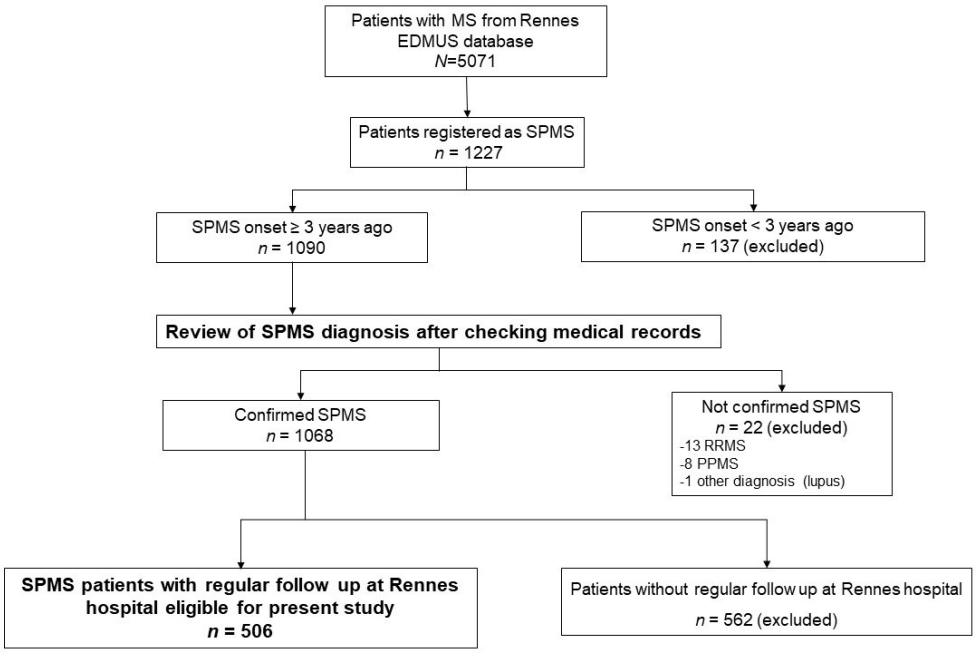

figure 1

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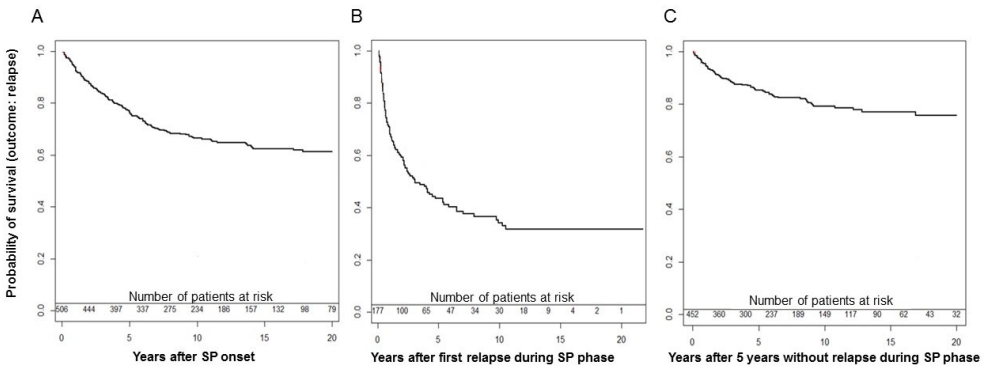

figure 2

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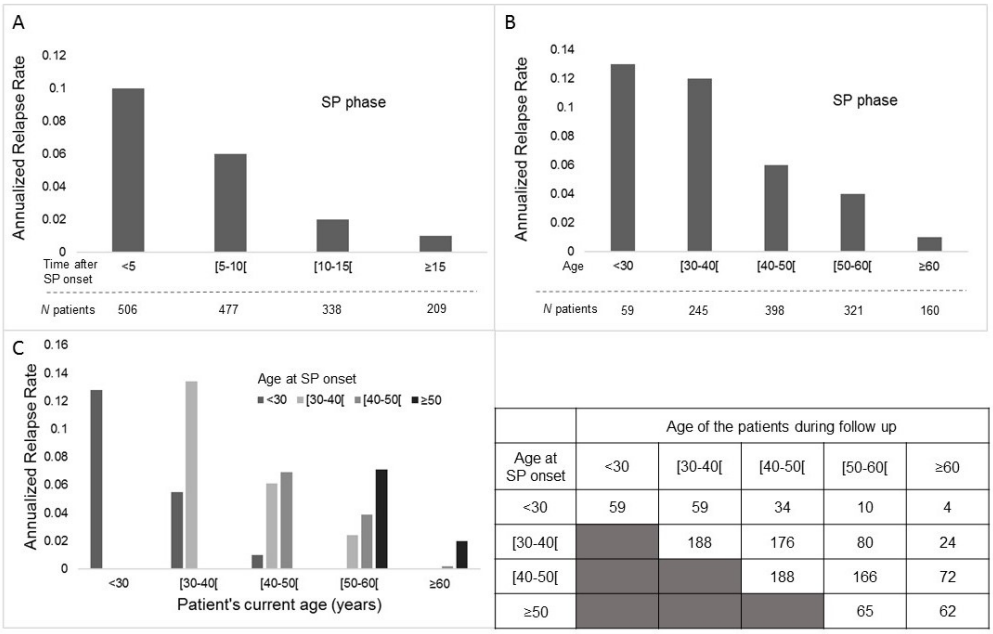
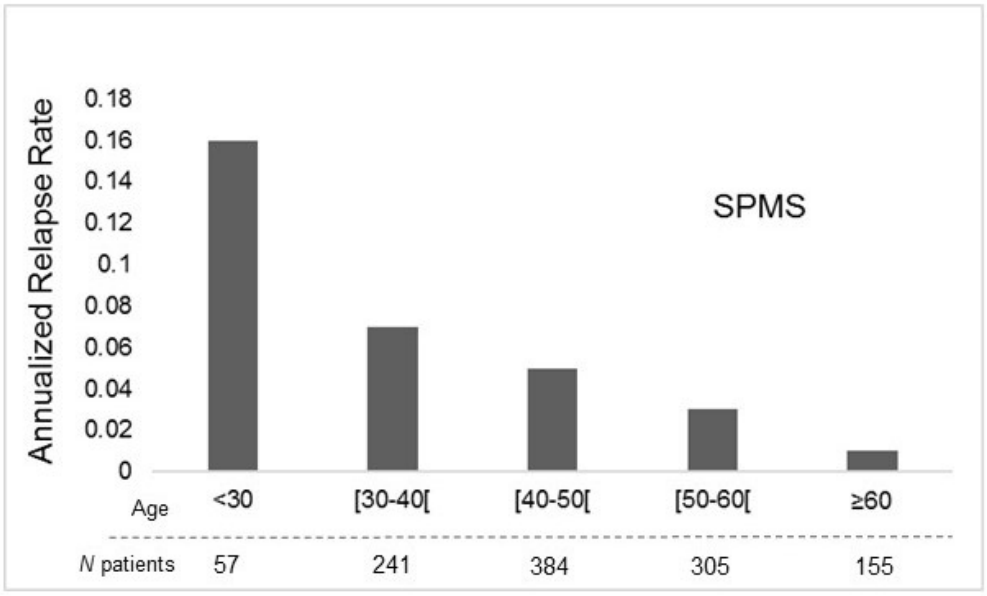


	Age of the patients during follow up				
Age at SP onset	<30	[30-40[	[40-50[	[50-60[	≥60
<30	59	59	34	10	4
[30-40[		188	176	80	24
[40-50[			188	166	72
≥50				65	62

figure 3

284x184mm (96 x 96 DPI)



supplementary figure e-1

161x99mm (96 x 96 DPI)

Supplementary Table 1: Factors associated with sustained disability progression during first 3 years after SP phase onset (479 patients)

Variable	Univariate analysis OR [95% CI]	*p*	Multivariate analysis OR [95% CI]	*p*
Age at SP phase onset*	0.92 [0.82, 1.04]	0.1844	Not significant	
Disease duration at SP phase onset*	0.92 [0.80, 1.06]	0.2449	Not included**	
At least 1 relapse between 0 and 3 years	2.94 [1.46, 5.89]	0.0024	3.12 [1.54, 6.31]	0.0016
EDSS score at SP phase onset	0.79 [0.67, 0.93]	0.0049	0.75 [0.63, 0.89]	0.0012
DMT between 0 and 3 years	1.85 [1.22, 2.79]	0.0036	Not significant	

*For 5 years.

** Factors associated with dependent variables with *p* values > 0.20 in the univariate analysis were not introduced in the multivariate analysis.

OR: odds ratio; 95% CI = confidence interval at 95%; EDSS = Expanded Disability Status Scale; SP = secondary progressive; DMT = disease modifying therapy.

Supplementary Table 2: Factors associated with sustained disability progression 3-5 years after SP phase onset (458 patients)

Variable	OR [95% CI]	*p*	OR [95% CI]	*p*
Age at SP phase onset*	0.91 [0.82, 1.01]	0.09	Not significant	
Disease duration at SP phase onset*	0.84 [0.74, 0.96]	0.01	0.97 [0.94, 1.00]	0.02
At least 1 relapse between 3 and 5 years	2.14 [1.23, 3.73]	0.008	2.04 [1.16, 3.58]	0.013
EDSS score at 3 years	0.86 [0.75, 0.99]	0.03	0.87 [0.76, 0.99]	0.04
DMTs between 3 and 5 years	1.06 [0.73, 1.55]	0.75	Not included**	

* For 5 years.

** Factors associated with dependent variables with *p* values > 0.20 in the univariate analysis were not introduced in the multivariate analysis.

OR: odds ratio; 95% CI = confidence interval at 95%; EDSS = Expanded Disability Status Scale; SP = secondary progressive; DMT = disease modifying therapy.

Supplementary Table 3: Factors associated with sustained disability progression 5-10 years after SP phase onset (347 patients)

Variable	OR [95% CI]	*p*	OR [95% CI]	*p*
Age at SP phase onset*	0.93 [0.81, 1.07]	0.3	Not included**	
Disease duration at SP phase onset*	0.81 [0.70, 0.94]	0.007	0.96 [0.93, 0.99]	0.007
At least 1 relapse between 5 and 10 years	1.27 [0.70, 2.30]	0.43	Not included**	
EDSS score at 5 years	0.81 [0.67, 0.97]	0.02	0.81 [0.67, 0.97]	0.02
DMTs between 5 and 10 years	1.51 [0.94, 2.42]	0.09	Not significant	

*For 5 years

** Factors associated with dependent variables with *p* values > 0.20 in the univariate analysis were not introduced in the multivariate analysis.

OR: odds ratio; 95% CI = confidence interval at 95%; EDSS = Expanded Disability Status Scale; SP = secondary progressive; DMT = disease modifying therapy.

Supplementary Table 4: Factors associated with sustained disability progression 10-15 years after SP phase onset (*n* = 208 patients)

Variable	OR [95% CI]	*p*	OR [95% CI]	*p*
Age at SP phase onset*	0.93 [0.77, 1.11]	0.4	Not included**	
Disease duration at SP phase onset*	0.92 [0.74, 1.14]	0.4	Not included**	
At least 1 relapse between 10 and 15 years	1.21 [0.45, 3.27]	0.7	Not included**	
EDSS score at 10 years	0.95 [0.74, 1.22]	0.7	Not included**	
DMTs between 10 and 15 years	1.52 [0.79, 2.91]	0.2	Not significant	

*For 5 years

**Factors associated with dependent variables with *p* values > 0.20 in the univariate analysis were not introduced in the multivariate analysis.

OR: odds ratio; 95% CI = confidence interval at 95%; EDSS = Expanded Disability Status Scale; SP = secondary progressive; DMT = disease modifying therapy.

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