



HAL
open science

Decreasing impact of late relapses on disability worsening in secondary progressive multiple sclerosis

Kevin Ahrweiller, Chloé Rousseau, Emmanuelle Le Page, Emma Bajoux, Emmanuelle Leray, Laure Michel, Gilles Edan, Anne Kerbrat

► **To cite this version:**

Kevin Ahrweiller, Chloé Rousseau, Emmanuelle Le Page, Emma Bajoux, Emmanuelle Leray, et al.. Decreasing impact of late relapses on disability worsening in secondary progressive multiple sclerosis. Multiple Sclerosis Journal, 2020, 26 (8), pp.924-935. 10.1177/1352458519848090 . hal-02150346

HAL Id: hal-02150346

<https://univ-rennes.hal.science/hal-02150346>

Submitted on 1 Jul 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1
2
3 **Decreasing impact of late relapses on disability worsening in secondary**
4
5
6 **progressive multiple sclerosis**
7
8

9 Kevin Ahrweiller MD¹, Chloé Rousseau², Emmanuelle Le Page MD^{1,3,4}, Emma Bajoux MD⁵,
10
11 Emmanuelle Leray PhD⁶, Laure Michel MD PhD⁷, Gilles Edan MD PhD^{1,3,4*}, Anne Kerbrat
12
13 MD^{1,4}
14
15

16
17 ¹Department of Neurology, University Hospital, Rennes, France; ²Clinical Investigation
18
19 Center (CIC-P) INSERM 1414, Department of Clinical Pharmacology, University Hospital,
20
21 Rennes, France; ³CIC-P INSERM 1414, University Hospital, Rennes, France; ⁴West
22
23 Neuroscience Network of Excellence (WENNE), France; ⁵Department of Epidemiology and
24
25 Public Health, University Hospital, Rennes, France; ⁶Ecole des Hautes Etudes en Santé
26
27 Publique (EHESP), Rennes, France; ⁷Department of Neurology, University Hospital, Nantes,
28
29 France
30
31
32

33
34 ***Corresponding author:** Prof. Gilles Edan, CHU Hôpital Pontchaillou, 2 rue Henri Le
35
36 Guilloux, 35033 Rennes Cedex 9, France; email: gilles.edan@chu-rennes.fr; Phone: + 33 (0)2
37
38 99 28 41 22; Fax: + 33 (0)2 99 28 41 32
39
40

41
42 **Number of reference: 35**
43

44 **Number of tables: 6**

Number of figures: 3

45 **Word count abstract: 199**

Word count paper: 3490

46 **Supplementary data: 4 Table and 1 Figure**
47

48 Statistical analysis was conducted by C. Rousseau (University Hospital, Rennes)

49 **Keywords: multiple sclerosis, secondary progressive, relapses, natural history, long-**
50
51 **term follow up**
52
53
54
55
56
57
58
59
60

Author contributions

K. Ahrweiller, study concept and design, acquisition of data, analysis and interpretation of data, critical revision of manuscript for intellectual content

C. Rousseau, statistical analysis

E. Le Page, critical revision of manuscript for intellectual content, analysis and interpretation of data, study concept and design

E. Bajoux, analysis and interpretation of data, critical revision of manuscript for intellectual content

E. Leray, critical revision of manuscript for intellectual content, analysis and interpretation of data

L. Michel, critical revision of manuscript for intellectual content

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

Author disclosure

K. Ahrweiller reports no disclosures

C. Rousseau reports no disclosures

E. Le Page reports consultancy fees and non-personal research grants from Novartis, Biogen-Idex, Teva, and Genzyme Sanofi Aventis.

E. Bajoux reports no disclosures

E. Leray reports no disclosures

L. Michel reports no disclosures

G. Edan reports grants and personal fees from Merck Serono, grants and personal fees from Teva Pharma, personal fees from Biogen, grants and personal fees from Novartis, personal fees from Sanofi.

A. Kerbrat reports personal fees from Novartis, Roche, Teva and Merck.

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.

1
2
3 The aims of the present study were therefore to i) describe changes in relapse frequency in an
4 SPMS population during long-term follow up with regular clinical examinations, ii) identify
5 predictive factors for relapse persistence during SPMS, and iii) assess the impact of relapses
6 on disability worsening, depending on the timing of their occurrence after SP phase onset.
7
8
9
10
11

12 13 **METHODS**

14 15 **Database**

16 All our patients were diagnosed according to Poser's classification [24]. They were identified
17 through the Rennes MS clinic database, which uses European Database for Multiple Sclerosis
18 (EDMUS) software [25] and was set up in January 1976. Since that date, all new cases of MS
19 have been systematically registered in the database. Historical data (date of clinical onset,
20 relapses, disability and treatment) were retrospectively obtained from records of the patients'
21 first visit. Follow-up data were then prospectively collected. For the present study, data were
22 extracted from the database on 1 March 2017. The database was approved by the French data
23 protection authority (CNIL).
24
25
26
27
28
29
30
31
32
33
34
35

36 37 **Patient selection**

38 Patients were retrospectively selected according to three inclusion criteria. i) They had to have
39 a diagnosis of SPMS, established by an MS specialist neurologist and defined as a history of
40 gradual worsening, after an initial relapsing disease course, with or without acute
41 exacerbations during the progressive course [1]. The date of transition to SPMS entered in the
42 database was systematically checked in the patients' medical records. ii) The SPMS
43 phenotype had to have lasted for at least 3 years, in order to have sufficient time to clearly
44 assess the disease course. iii) Patients had to undergo regular follow up at the Rennes MS
45 clinic. They were typically assessed once a year. We excluded patients who were only
46 occasionally referred from other centres for an expert judgment (Figure 1).
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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, alemtuzumab) 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). ARR (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

1
2
3 were transformed into categorical variables. Results were expressed as hazard ratios (HRs)
4
5 with 95% CIs.
6
7

8 The same analysis was conducted to explain time to EDSS 6, introducing the occurrence of at
9
10 least one relapse during the SP phase but before EDSS 6 as an additional potential
11
12 explanatory factor. This factor and the use of DMTs were considered as time-dependent
13
14 variables. Patients who reached EDSS 6 before onset of progression were excluded for this
15
16 analysis.
17
18
19

20 To look for a potential link between clinical disease activity and short-term disability
21
22 progression, we divided the SP phase into four periods (first 3 years, 3-5 years, 5-10 years,
23
24 and 10-15 years after SP phase onset). We then built a logistic regression model to identify
25
26 factors associated with irreversible disability worsening for each period, which was
27
28 independently analysed. Disability progression in each period was defined as an increase in
29
30 the EDSS score of at least 1 point if the baseline EDSS was 5.5 or less, and 0.5 point if the
31
32 baseline EDSS was more than 5.5.
33
34
35
36

37 Results were expressed as odds ratios (ORs) with 95% CIs. For each model, factors associated
38
39 with dependent variables with p values < 0.20 in the univariate analysis were introduced in
40
41 the multivariate analysis, and backward selection was then applied. P values below 0.05 for
42
43 two-tailed tests were considered to be statistically significant. Statistical analyses were
44
45 performed with SAS software (V. 9.4).
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 age at SP onset and patient's current age at relapse occurrence (i.e. disease duration) into
4 account. Both factors influenced the ARR. For example, if a patient was currently aged 50-60
5 years and had just entered the SP phase (SP onset after 50 years in Fig. 3C), his or her ARR
6 was about 0.07. However, if a patient of the same age had entered the SP phase 20 years
7 earlier (SP onset at 30-40 years in Fig. 3C), his or her ARR was just 0.02.
8
9

10
11
12
13
14
15 The direction of findings did not differ when ARRs were calculated after removing the period
16 of follow up spent on DMT, corresponding to 39.3% of total follow-up duration during SPMS
17 (Supplementary Fig. 1).
18
19
20
21
22

23 **Factors associated with relapse occurrence during SP phase**

24
25 The results are detailed in Table 3. In the univariate analysis, the following factors were
26 associated with relapse occurrence during the SP phase: i) shorter disease duration ($p =$
27 0.004); ii) younger age at SP onset ($p = 0.0001$); and iii) DMT ($p = 0.03$). In the multivariate
28 analysis, the patient's age at SP onset was the only significant parameter (HR = 0.97, 95% CI
29 [0.95, 0.98], $p = 0.0001$). DMT duration (< 1 year, 1-3 years, 3-5 years or > 5 years, and > or
30 < 3.4 years during the first 5 years of the SP phase) was not associated with relapse
31 occurrence. Treatment by immunomodulator rather than immunosuppressant was associated
32 with relapse (HR = 1.83 [1.13; 2.97]).
33
34
35
36
37
38
39
40
41
42
43

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

45
46
47 The results are detailed in Table 4. The median time from SP onset to EDSS 6 was 6.7 years.
48 Relapse occurrence after SP onset was significantly associated with a shorter time from SP
49 onset to EDSS 6 in the multivariate analysis (HR = 1.30, 95% CI [1.02, 1.66], $p = 0.03$). A
50 higher EDSS score at SP phase onset and DMTs during the SP phase were also associated
51 with a shorter time from SP phase onset to EDSS 6 ($p < 0.0001$ and $p = 0.001$).
52
53
54
55
56
57
58
59
60

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

1
2
3 patients with a low or high risk of clinical inflammatory activity during the SP phase. Finally,
4
5 in our study, we found higher relapse frequency than a previous study in SPMS [23] after age
6
7 55 years (12.8% vs. 4.8%) and after 5 years of SPMS (36.7% vs. 8.4%). This discrepancy can
8
9 probably be attributed to the longer duration of follow up in our population.
10
11
12
13
14

15 **Relapses and disability progression**

16
17 Earlier natural history studies [31–33] had found no influence of relapses on disability
18
19 worsening during the SP phase, but a more recent study [23] reported conflicting results.
20
21 These studies are summarized in Table 6. Different outcomes and analyses were used in these
22
23 studies, making it difficult to compare the results. However, the more recent study [23] used
24
25 an analysis and outcome (time from SP onset to EDSS 6) similar to ours, as well as a similar
26
27 number of patients, and reached the same conclusion (i.e. association between relapse
28
29 occurrence during SPMS and time from SP phase onset to EDSS 6). Interestingly, our second
30
31 analysis dividing the SP phase into four periods nuanced this result, and possibly provided an
32
33 explanation for the earlier negative studies. More specifically, we only found a positive
34
35 association for relapse occurrence and irreversible disability worsening during the first 5 years
36
37 of SPMS, and not during the subsequent 10 years. Our interpretation of these results is that
38
39 relapses occurring during the first years of SPMS still have a significant impact on disability
40
41 worsening, whereas in the later stages of SPMS, the occurrence of relapses have a lower
42
43 impact. Another degenerative process, independent of focal inflammation might become
44
45 predominant [29].
46
47
48
49
50
51

52
53 Concerning the potential impact of treatment, in our study, DMTs for at least 3 months during
54
55 SPMS were associated with a shorter time from SP onset to EDSS 6. Similarly, we found a
56
57 positive association between relapse occurrence during the SP phase and DMTs for at least 3
58
59 months. This apparently *paradoxical* results probably reflect the fact that patients with
60

1
2
3 persistent relapses and more severe disease were more likely to be treated and is consistent
4 with a previous study [23]. It also suggests that the patients with SPMS who had persistent
5 relapses under treatment represented a particular subgroup of patients with a more severe
6 disease course. However, we need to emphasise that our study was not designed to assess the
7 impact of DMTs on relapses or disability worsening, and methodological issues prevent us
8 from reaching any firm conclusions in this respect. The patients were treated with a wide
9 variety of drugs, in different combinations and for varying durations, which prevented us from
10 comparing different therapeutic strategies.
11
12
13
14
15
16
17
18
19
20

21 **Limitations**

22
23
24
25 First, pinpointing when SPMS starts is obviously difficult. In our study, we used the
26 definition of the recently proposed classification of progressive MS [1]. SPMS was
27 retrospectively diagnosed by MS specialist neurologists who followed the patients on a yearly
28 basis and was based on a history of gradual worsening after an initial relapsing disease course.
29 It should be noted that in our jurisdiction, diagnosis of SPMS does not deprive patients of
30 access to DMTs, and so does not influence neurologists' clinical reports. Moreover, the SPMS
31 phenotype had to have lasted for at least 3 years, in order to have sufficient time to clearly
32 assess the disease course, and the date of the diagnosis was systematically reviewed in the
33 patient's medical records. Another definition of SPMS using EDSS score criteria was recently
34 proposed [34]. This definition required a minimum EDSS score of 4 and a minimum
35 pyramidal functional score of 2. In our study, the EDSS score at SPMS diagnosis was lower
36 than in the proposed definition (median EDSS score = 3), but was similar to other studies
37 [15,23]. The MS specialist neurologists probably detected subtle forms of progression in our
38 cohort before EDSS 4. Second, another limitation in our study might concern relapse
39 diagnosis in SP phase: identifying relapses in a condition in which disability can vary from
40 day to day and according to different processes is a challenge both for the neurologist and for
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 the patient. Thus, the frequency of relapse could have been underestimated in our study. On
4
5 one hand, patients with SPMS probably consult less for minor or moderate neurological
6
7 symptoms, and could forget to mention them at the yearly follow-up visit. On the other hand,
8
9 relapses were assessed mostly on clinical grounds in our study, as MRI data were not
10
11 systematically available. Thus, it could have been difficult for the neurologist to confirm a
12
13 relapse, especially retrospectively, based on patient interview. To partly overcome this
14
15 limitation, these critical data were systematically checked in the patients' medical records.
16
17 Moreover, in order to emphasize a prospective collection of these data, we chose to exclude
18
19 from our analysis 562 patients without regular follow up. When we compared patients who
20
21 had been included in the study with those who had been excluded, we found that they had
22
23 similar demographic characteristics. Third, a large proportion of our patients were treated,
24
25 preventing us from reporting a true natural history of MS. However, the direction of our
26
27 findings on the ARR did not differ when analyses were repeated after removing data collected
28
29 under DMTs (supplementary Fig. 1). Fourth, the unequal changes between the EDSS steps
30
31 [35] are a potential confounding factor. Patients with lower EDSS scores during early SPMS
32
33 are more likely to progress than patients with higher EDSS scores. This point was illustrated
34
35 in our study by the significant association between a lower EDSS score and an EDSS score
36
37 increase in each period (Supplementary Fig. 1-4). From 4 onwards, the EDSS score relies
38
39 mainly on lower limb function, with the other functions contributing less. Consequently, the
40
41 effect of relapses on these functions later on in the disease is more difficult to evaluate.
42
43
44
45
46
47
48
49

50 **Conclusion and perspectives**

51
52 Despite these limitations, the present study yielded arguments in favour of a relationship
53
54 between relapse occurrence during early SPMS and short-term disability worsening, but
55
56 suggested that late relapses do not have a decisive impact on disability progression in SPMS.
57
58 Moreover, it was the youngest patients with the most persistent focal activity who were the
59
60

1
2
3 most concerned. Thus, if the use of DMTs would appear to be more justified in younger
4
5 patients with early SPMS, the continuation of DMTs in older patients with SPMS may result
6
7 in adverse effects outweighing any possible benefits of the drugs. Overall, given the small
8
9 effect of relapses on disability accumulation, the risk-benefit ratio of therapy should be
10
11 carefully considered.
12
13
14
15
16
17
18
19
20
21
22

23 ACKNOWLEDGEMENTS

24
25 We thank the Observatoire Français de la Sclérose en Plaques (OFSEP) for financially
26
27 supporting the data manager (Damien Le Port) who updated our database.
28
29
30

31 REFERENCES

- 32
33
34
35
36 1. Lublin FD, Reingold SC, Cohen JA et al. Defining the clinical course of multiple
37 sclerosis: the 2013 revisions. *Neurology* 2014 Jul 15;83(3):278–86.
38
39 2. Filippini G, Del Giovane C, Vacchi L et al. Immunomodulators and
40 immunosuppressants for multiple sclerosis: a network meta-analysis. *Cochrane*
41 *Database Syst Rev* 2013 Jun 6;(6):CD008933.
42
43 3. Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-Beta-1a in MS
44 (SPECTRIMS) Study Group. Randomized controlled trial of interferon- beta-1a in
45 secondary progressive MS: Clinical results. *Neurology* 2001 Jun 12;56(11):1496–504.
46
47 4. Panitch H, Miller A, Paty D et al. North American Study Group on Interferon beta-1b in
48 Secondary Progressive MS. Interferon beta-1b in secondary progressive MS: results
49 from a 3-year controlled study. *Neurology* 2004 Nov 23;63(10):1788–95.
50
51 5. Cohen JA, Cutter GR, Fischer JS et al. Benefit of interferon beta-1a on MSFC
52 progression in secondary progressive MS. *Neurology* 2002 Sep 10;59(5):679–87.
53
54 6. Andersen O, Elovaara I, Färkkilä M et al. Multicentre, randomised, double blind,
55 placebo controlled, phase III study of weekly, low dose, subcutaneous interferon beta-1a
56 in secondary progressive multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2004
57 May;75(5):706–10.
58
59
60

- 1
2
3 7. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability
4 status scale (EDSS). *Neurology* 1983 Nov;33(11):1444–52.
- 5
6 8. European Study Group on interferon beta-1b in secondary progressive MS. Placebo-
7 controlled multicentre randomised trial of interferon beta-1b in treatment of secondary
8 progressive multiple sclerosis. *Lancet Lond Engl* 1998 Nov 7;352(9139):1491–7.
- 9
10 9. Kappos L, Bar-Or A, Cree BAC et al. Siponimod versus placebo in secondary
11 progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study.
12 *The Lancet* 2018 Mar;391(10127):1263–73.
- 13
14 10. Montalban X, Hauser SL, Kappos L et al. Ocrelizumab versus Placebo in Primary
15 Progressive Multiple Sclerosis. *N Engl J Med* 2017 19;376(3):209–20.
- 16
17 11. Hawker K, O'Connor P, Freedman MS et al. Rituximab in patients with primary
18 progressive multiple sclerosis: results of a randomized double-blind placebo-controlled
19 multicenter trial. *Ann Neurol* 2009 Oct;66(4):460–71.
- 20
21 12. Loneragan R, Kinsella K, Duggan M et al. Discontinuing disease-modifying therapy in
22 progressive multiple sclerosis: can we stop what we have started? *Mult Scler Houndmills
23 Basingstoke Engl* 2009 Dec;15(12):1528–31.
- 24
25 13. Bonenfant J, Bajeux E, Deburghgraeve V et al. Can we stop immunomodulatory
26 treatments in secondary progressive multiple sclerosis? *Eur J Neurol* 2017
27 Feb;24(2):237–44.
- 28
29 14. Scalfari A, Neuhaus A, Daumer M et al. Early relapses, onset of progression, and late
30 outcome in multiple sclerosis. *JAMA Neurol* 2013 Feb;70(2):214–22.
- 31
32 15. Scalfari A, Neuhaus A, Degenhardt A et al. The natural history of multiple sclerosis: a
33 geographically based study 10: relapses and long-term disability. *Brain J Neurol* 2010
34 Jul;133(Pt 7):1914–29.
- 35
36 16. Novotna M, Paz Soldán MM, Abou Zeid N et al. Poor early relapse recovery affects
37 onset of progressive disease course in multiple sclerosis. *Neurology* 2015 Aug
38 25;85(8):722–9.
- 39
40 17. Bsteh G, Ehling R, Lutterotti A et al. Long Term Clinical Prognostic Factors in
41 Relapsing-Remitting Multiple Sclerosis: Insights from a 10-Year Observational Study.
42 *PloS One* 2016;11(7):e0158978.
- 43
44 18. Glad SB, Nyland HI, Aarseth JH et al. Long-term follow-up of benign multiple sclerosis
45 in Hordaland County, Western Norway. *Mult Scler Houndmills Basingstoke Engl* 2009
46 Aug;15(8):942–50.
- 47
48 19. Bergamaschi R, Berzuini C, Romani A et al. Predicting secondary progression in
49 relapsing-remitting multiple sclerosis: a Bayesian analysis. *J Neurol Sci* 2001 Aug
50 15;189(1–2):13–21.
- 51
52 20. Leray E, Yaouanq J, Le Page E et al. Evidence for a two-stage disability progression in
53 multiple sclerosis. *Brain J Neurol* 2010 Jul;133(Pt 7):1900–13.
- 54
55
56
57
58
59
60

- 1
2
3 21. Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of
4 irreversible disability in multiple sclerosis: an amnesic process. *Brain J Neurol* 2003
5 Apr;126(Pt 4):770–82.
- 6
7 22. Tremlett H, Zhao Y, Joseph J et al. Relapses in multiple sclerosis are age- and time-
8 dependent. *J Neurol Neurosurg Psychiatry* 2008 Dec;79(12):1368–74.
- 9
10 23. Paz Soldán MM, Novotna M, Abou Zeid N et al. Relapses and disability accumulation in
11 progressive multiple sclerosis. *Neurology* 2015 Jan 6;84(1):81–8.
- 12
13 24. Poser CM, Paty DW, Scheinberg L et al. New diagnostic criteria for multiple sclerosis:
14 guidelines for research protocols. *Ann Neurol* 1983 Mar;13(3):227–31.
- 15
16 25. Confavreux C, Compston DA, Hommes OR et al. EDMUS, a European database for
17 multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 1992 Aug;55(8):671–6.
- 18
19 26. Broman T, Andersen O, Bergmann L. Clinical studies on multiple sclerosis. I.
20 Presentation of an incidence material from Gothenburg. *Acta Neurol Scand* 1981
21 Jan;63(1):6–33.
- 22
23 27. Skoog B, Runmarker B, Winblad S et al. A representative cohort of patients with non-
24 progressive multiple sclerosis at the age of normal life expectancy. *Brain J Neurol* 2012
25 Mar;135(Pt 3):900–11.
- 26
27 28. Tortorella C, Bellacosa A, Paolicelli D et al. Age-related gadolinium-enhancement of
28 MRI brain lesions in multiple sclerosis. *J Neurol Sci* 2005 Dec 15;239(1):95–9
- 29
30 29. Frischer JM, Weigand SD, Guo Y et al. Clinical and pathological insights into the
31 dynamic nature of the white matter multiple sclerosis plaque. *Ann Neurol* 2015
32 Nov;78(5):710–21.
- 33
34 30. Steiner D, Arnold DL, Freedman MS et al. Natalizumab versus placebo in patients with
35 secondary progressive Multiple Sclerosis: Results from ascend, a multicenter, double-
36 blind, placebo-controlled, randomized phase 3 trial. Oral presentation, AAN 2016.
- 37
38 31. Confavreux C, Vukusic S. Relapses and progression of disability in multiple sclerosis. *N*
39 *Engl J Med* 2000 Nov 16;343(20):1430–8.
- 40
41 32. Tremlett H, Yousefi M, Devonshire V et al. Impact of multiple sclerosis relapses on
42 progression diminishes with time. *Neurology* 2009 Nov 17;73(20):1616–23.
- 43
44 33. Kremenchutzky M, Rice GPA, Baskerville J et al. The natural history of multiple
45 sclerosis: a geographically based study 9: observations on the progressive phase of the
46 disease. *Brain J Neurol* 2006 Mar;129(Pt 3):584–94.
- 47
48 34. Lorscheider J, Buzzard K, Jokubaitis V et al. Defining secondary progressive multiple
49 sclerosis. *Brain J Neurol* 2016 Sep;139(Pt 9):2395–405.
- 50
51 35. Kragt JJ, Thompson AJ, Montalban X et al. Responsiveness and predictive value of
52 EDSS and MSFC in primary progressive MS. *Neurology* 2008 Mar 25;70(13 Pt
53 2):1084–91.
- 54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1: Baseline characteristics of the secondary progressive MS population

Characteristics	SPMS population
<i>Number of patients (%)</i>	506
<i>Sex</i>	
Women (%)	320 (63.2)
<i>Follow up duration during SP phase in years (mean ± SD)</i>	14.3 (7.3)
<i>Disease progression</i>	
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
<i>Treatment during SP phase</i>	
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
<i>Type of treatment (no. patients, %)</i>	

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)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

Characteristics	SPMS population		<i>p</i> *
	SPMS patients with at least one relapse	SPMS patients without relapse	
<i>Number of patients (%)</i>	177 (35.0)	329 (65.0)	
<i>Sex</i>			
Women (%)	111 (62.7)	209 (63.5)	0.90
<i>Follow up duration during SP phase in years (mean ± SD)</i>	13.8 (6.1)	14.5 (7.8)	0.30
<i>Disease progression</i>			
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
<i>Treatment during SP phase</i>			
Number of treated patients (%)	159 (89.8)	246 (74.8)	0.04

Treatment duration in years (mean \pm SD)	5.8 \pm 4	4.9 \pm 4	0.04
Percentage of time under treatment (mean \pm SD)	43.3 \pm 24.4	36.6 \pm 25.6	0.01
<i>EDSS scores during SP phase</i>			
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
<i>Relapse phenotype (%)</i>			
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		
<i>Relapse with incomplete recovery (%)</i>			
	39.7		

<i>Relapse with brain MRI scan within 6 month (%)</i>	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 $p < 0.05$.*

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

	Study population (<i>N</i> = 506)	Patients with relapse(s) (<i>n</i> = 177)	Univariate analysis		Multivariate analysis	
			HR [95% CI]	<i>P</i>	HR [95% CI]	<i>P</i>
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]			

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 States)	533	Time from PPO to EDSS 6	Study of influence of relapses occurring after PPO on time from PPO to EDSS 6	Reduced time to EDSS 6 associated with relapses

1
2

3 States)			EDSS 6 (survival analysis)	
4				
5				
6 Kremenchutzky et al., 7 Brain 2006** 8 (London, Ontario, 9 Canada)	286	Time from PPO to EDSS 6, 8 and 10	Comparison between SAP and SP	No difference between groups
10				
11				
12				
13 Scalfari et al., Brain 14 2010** 15 (London, Ontario, 16 Canada)	534	Time from PPO 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
17				
18				
19				
20				
21				

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

25 ***Patients with RRMS and SPMS were included**

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

27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **Figure 1: Selection of patients from the Rennes MS clinic EDMUS database**

4
5 *EDMUS: European Database for Multiple Sclerosis; EDSS: Expanded Disability Status Scale;*
6
7 *RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis;*
8
9 *PPMS: primary progressive multiple sclerosis.*

10
11
12
13
14 **Figure 2: Relapse occurrence during secondary progressive MS phase: (A)** Time from
15
16 SPMS onset to first relapse ($n = 506$ patients), **(B)** Time from first relapse to second relapse ($n =$
17
18 177 patients), **(C)** Time from first 5 years without relapse during SPMS to subsequent relapse ($n =$
19
20 452 patients).

21
22
23
24 **Figure 3: Annualized relapse rate according to patient's current age, disease duration**
25
26 **and age at secondary progressive onset: (A)** time after SP (secondary progressive) phase
27
28 onset, **(B)** patient's current age, **(C)** patient's current age and patient's age at SP onset. The number
29
30 of patients in each group is detailed in the table.

31
32
33
34
35 *Annualised relapse rate = (relapse count/number of days indicated by each patient) x 365.25.*

36
37
38 **Figure e-1: Annualized relapse rate according to patient's current age after removing**
39
40 **time spent on disease modifying treatments**

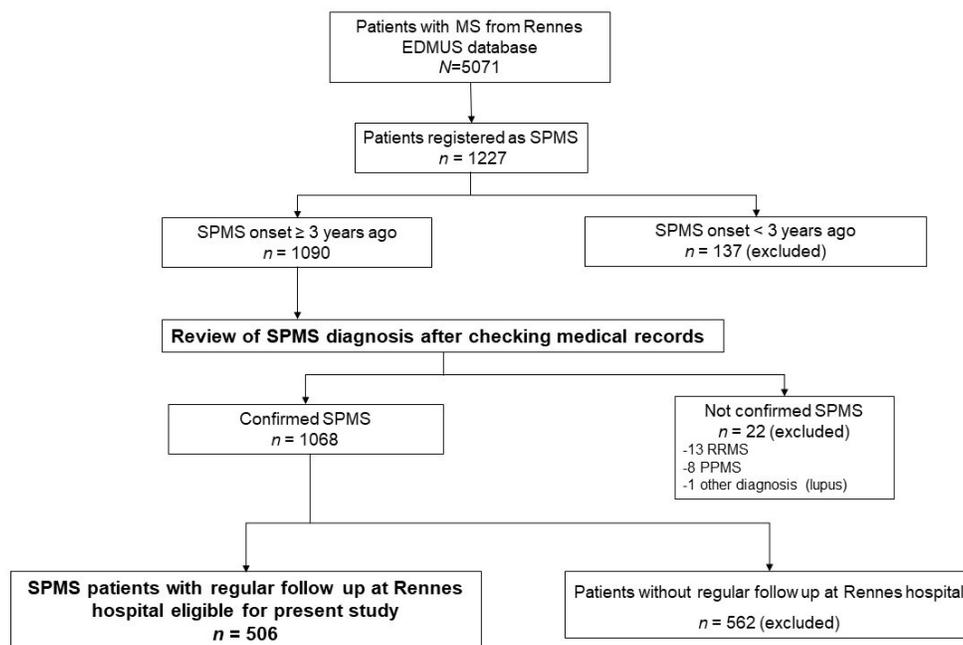


figure 1

292x190mm (96 x 96 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

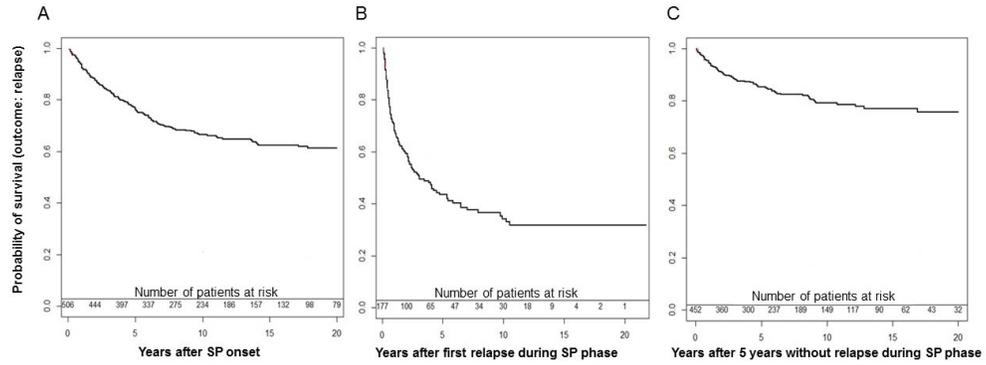


figure 2

334x125mm (96 x 96 DPI)

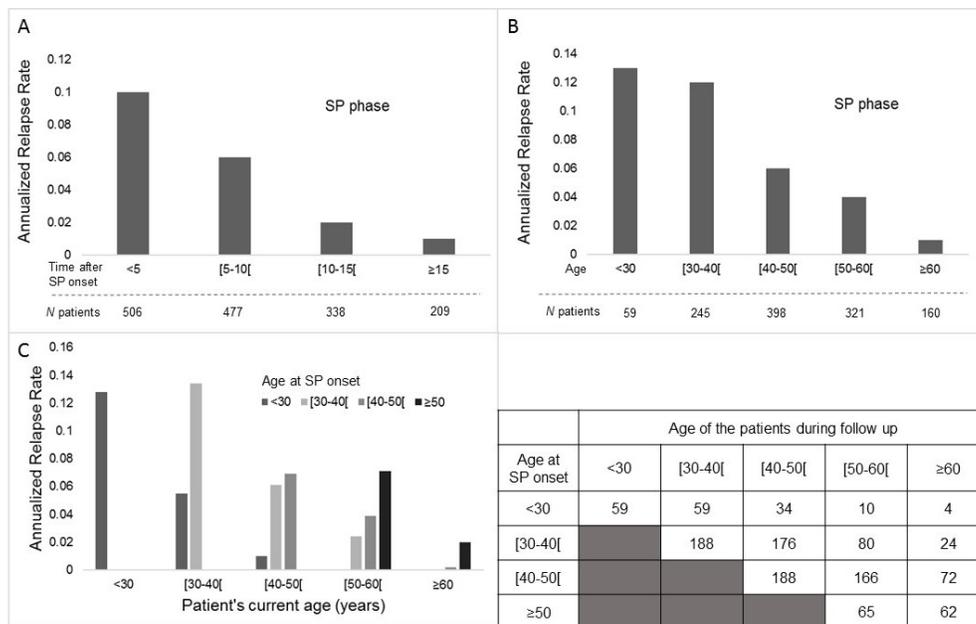
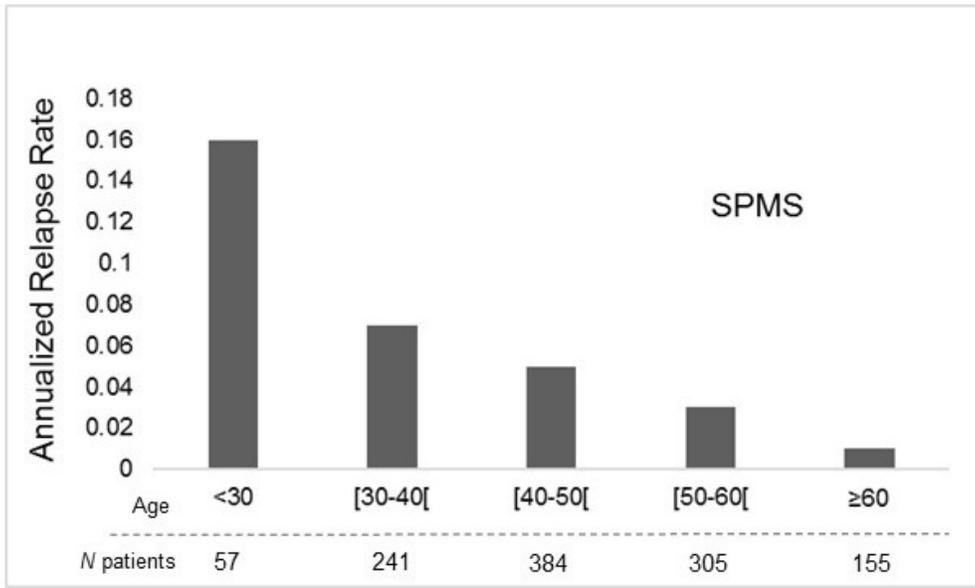


figure 3

284x184mm (96 x 96 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



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		Multivariate analysis	
	OR [95% CI]	<i>p</i>	OR [95% CI]	<i>p</i>
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]	<i>p</i>	OR [95% CI]	<i>p</i>
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]	<i>p</i>	OR [95% CI]	<i>p</i>
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]	<i>p</i>	OR [95% CI]	<i>p</i>
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.

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60