

Supplementary Materials

Supplementary Table 1. SEL- and PRL-derived metrics at the patient level in the short- and long-time range interval sub-cohorts

	Patients followed-up for < 2 years [n=15]	Patients followed-up for ≥ 2 years [n=46]	p value*
Total lesions count at baseline (n), median [range]	18 [2 – 80]	20 [1 – 77]	0.750
SEL count at baseline (n), median [range]	5 [0 – 41]	5 [0 – 41]	0.960
Non-SEL count at baseline (n), median [range]	16 [1 – 55]	9 [0 – 50]	0.580
PRL count at baseline (n), median [range]	1 [0 – 6]	1 [0 – 8]	0.750
Total lesion volume at baseline (ml), median [range]	2.3 [0.1 – 9.7]	2.1 [0.1 – 66.9]	0.624
SEL volume at baseline (ml), median [range]	0.6 [0 – 3.8]	0.6 [0 – 65.3]	0.496
Non-SEL volume at baseline (ml), median [range]	1.6 [0.1 – 6.4]	0.9 [0 – 27.1]	0.863
PRL volume at baseline (ml), median [range]	0.1 [0 – 0.8]	0.1 [0 – 1.0]	0.828

*unpaired sample t-test (for the normally distributed variables) or Mann-Whitney test (for the non-normally distributed variables)

Supplementary Table 2. Treatment status in the patient categories according to SELs and PRLs combinations

	All patients (n=61)	SEL+PRL+ (n=31)	SEL+PRL- (n=25)	SEL- (n=5)
Treated at baseline, n (%)	16 (26%)	13 (42%)	3 (12%)	0 (0%)
Treated at final scan, n (%)	51 (84%)	30 (97%)	16 (64%)	5 (100%)
Change from untreated to treated from baseline to final scan	35 (57%)	17 (55%)	13 (52%)	5 (100%)

The percentage of patients who changed from untreated to treated by the end of the study was not significantly different between SEL+PRL+ and SEL+PRL- groups ($p>0.05$).

Supplementary Table 3. SEL and PRL-derived metrics at the patient level in the group with or without a history of relapses ≤ 3 months before study entry.

	Patients without relapses within 3 months before study entry [n=41]	Patients with relapses within 3 months before study entry [n=20]	p value*
Total lesions count at baseline (n), median [range]	15 [1 – 80]	22 [3 – 66]	0.564
SEL count at baseline (n), median [range]	7 [0 – 41]	4.5 [0 – 39]	0.410
Non-SEL count at baseline (n), median [range]	7 [0 – 55]	16 [2 – 39]	0.183
PRL count at baseline (n), median [range]	1 [0 – 8]	1 [0 – 6]	0.565
Total lesion volume at baseline (ml), median [range]	2.0 [0.1 – 66.9]	2.6 [0.2 – 27.1]	0.783
SEL volume at baseline (ml), median [range]	0.7 [0 – 65.3]	0.4 [0 – 3.3]	0.535
Non-SEL volume at baseline (ml), median [range]	0.7 [0 – 13.9]	1.7 [0.1 – 27.1]	0.332
PRL volume at baseline (ml), median [range]	0.01 [0 – 1.0]	0.03 [0 – 1.0]	0.802
BPF median (range)	0.77 [0.72 – 0.79]	0.76 [0.74 – 0.79]	0.712

*unpaired sample t-test (for the normally distributed variables) or Mann-Whitney test (for the non-normally distributed variables)

Abbreviations: SEL= slowly expanding lesion; BPF = brain parenchymal fraction

Supplementary Table 4. SEL and PRL-derived metrics at the patient level in the group with ≥ 5 or < 5 gadolinium-enhancing lesions at study onset.

	Patients with < 5 gadolinium-enhancing lesions [n=54]	Patients with ≥ 5 gadolinium- enhancing lesions [n=7]	p value*
Total lesions count at baseline (n), median [range]	14.5 [1 – 80]	28 [21 – 54]	0.083
SEL count at baseline (n), median [range]	5 [0 – 41]	8 [0 – 23]	0.734
Non-SEL count at baseline (n), median [range]	7 [0 – 55]	23 [15 – 39]	0.011
PRL count at baseline (n), median [range]	1 [0 – 8]	1 [0 – 6]	0.543
Total lesion volume at baseline (ml), median [range]	1.80 [0.02 – 66.93]	3.25 [1.27 – 27.16]	0.066
SEL volume at baseline (ml), median [range]	0.49 [0 – 65.34]	0.68 [0 – 2.51]	0.767
Non-SEL volume at baseline (ml), median [range]	0.84 [0 – 13.94]	2.44 [0.90 – 27.14]	0.013
PRL volume at baseline (ml), median [range]	0.03 [0 – 0.99]	0.04 [0 – 1.00]	0.650
BPF median (range)	0.77 [0.72 – 0.79]	0.76 [0.74 – 0.79]	0.839

*unpaired sample t-test (for the normally distributed variables) or Mann-Whitney test (for the non-normally distributed variables)

Abbreviations: SEL= slowly expanding lesion; BPF = brain parenchymal fraction

Supplementary Table 5. Association between the SEL-PRL measures and categories with EDSS over time using mixed-effects regression models

	MRI and patient category (Independent variables)	EDSS (Dependent variable)	
Model	Interaction terms with time	Beta coefficient [95% CI]	p value
1	definite SEL count (n)	beta=0.01/year [0.001; 0.03]	p=0.045
2	definite SEL volume* (ml)	beta=0.01/year [0.001; 0.01]	p=0.044
3	SEL+ (category: binary)	beta=-0.01/year [-0.33,0.32]	p=0.974
4	PRL count at baseline (n)	beta=0.04/year [-0.01,0.08]	p=0.080
5	PRL volume* at baseline (ml)	beta=0.02/year [-0.001,0.05]	p=0.084
6	PRL+ (category: binary)	beta=0.15/year [0.01; 0.30]	p=0.044
7	SEL+PRL+ (category: binary)	beta=0.16/year [0.01; 0.31]	p=0.032
8	SEL- (category: binary)	beta=0.01/year [-0.32; 0.33]	p=0.974
9	definite SEL count (n)	beta= 0.01 [-0.002; 0.02]	p=0.109
	PRL+ (category: binary)	beta=0.10 [-0.05; 0.26]	p=0.193
10	definite SEL volumes* (ml)	beta=0.01 [-0.001; 0.01]	p=0.109
	PRL+ (category: binary)	beta=0.11 [-0.05; 0.26]	p=0.181
11	PRL+ (category: binary)	0.03 [-0.33; 0.39]	p=0.867
	SEL+PRL+ (category: binary)	0.14 [-0.23; 0.50]	p=0.461

*refers to the log-transformed volumes of the definite SEL category and the PRL category

The table shows the interaction terms between time and the independent variables,

MRI measures or patient categories, while the clinical score (EDSS) was the dependent variable. Whenever the interaction term is significant, we assume that there is a significant association between the MRI measure/patient category and the change in the clinical variable over time.

The following lines explain one by one all the models using the identification of the first column of the table:

Model 1

Dependent variable = EDSS

Explanatory variables = SEL count (n), time (in years)

Interaction term: time x SELs, Age (at baseline), Gender(male/female), Disease Duration, Total lesion volume, Treatment at end of study (yes/no), Number of relapses during observation

Model 2

Dependent variable = EDSS

Explanatory variables = SEL volume (ml), time (in years)

Interaction term: time x SELs, Age (at baseline), Gender(male/female), Disease Duration, Total lesion volume, Treatment at end of study (yes/no), Number of relapses during observation

Model 3

Dependent variable = EDSS

Explanatory variables = SEL+ (or ≥ 1 SEL) category (binary: yes/no)

Interaction term: time x SEL+, Age (at baseline), Gender(male/female), Disease Duration, Total lesion volume, Treatment at end of study (yes/no), Number of relapses during observation

Model 4

Dependent variable = EDSS

Explanatory variables = PRL count (n), time (in years)

Interaction term: time x PRL count, Age (at baseline), Gender(male/female), Disease Duration, Total lesion volume, Treatment at end of study (yes/no), Number of relapses during observation

Model 5

Dependent variable = EDSS

Explanatory variables = PRL volume (ml), time (in years)

Interaction term: time x PRL volume, Age (at baseline), Gender(male/female), Disease Duration, Total lesion volume, Treatment at end of study (yes/no), Number of relapses during observation

Model 6

Dependent variable = EDSS

Explanatory variables = PRL+ (or ≥ 1 PRL) category (binary: yes/no)

Interaction term: time x PRL+, Age (at baseline), Gender(male/female), Disease Duration, Total lesion volume, Treatment at end of study (yes/no), Number of relapses during observation

Model 7

Dependent variable = EDSS

Explanatory variables = SEL+PRL+ (or ≥ 1 SEL & ≥ 1 PRL) category (binary: yes/no)

Interaction term: time x SEL+PRL+, Age (at baseline), Gender(male/female), Disease Duration, Total lesion volume, Treatment at end of study (yes/no), Number of relapses during observation

Model 8

Dependent variable = EDSS

Explanatory variables = SEL- (or 0 SEL) category (binary: yes/no)

Interaction term: time x SEL-, Age (at baseline), Gender(male/female), Disease Duration, Total lesion volume, Treatment at end of study (yes/no), Number of relapses during observation

Model 9

Dependent variable = EDSS

Explanatory variables = SEL count (n), PRL+ category (binary: yes/no)

Interaction term: time x SEL count

Interaction term: time x PRL+, Age (at baseline), Gender (male/female), Disease Duration, Total lesion volume, Treatment at end of study (yes/no), Number of relapses during observation

Model 10

Dependent variable = EDSS

Explanatory variables = SEL volume (ml), PRL+ category (binary: yes/no)

Interaction term: time x SEL volume

Interaction term: time x PRL+, Age (at baseline), Gender(male/female), Disease Duration, Total lesion volume, Treatment at end of study (yes/no), Number of relapses during observation

Model 11

Dependent variable = EDSS

Explanatory variables = SEL+PRL+ category (binary: yes/no), PRL+ category (binary: yes/no)

Interaction term: time x SEL+PRL+, time x PRL+, Age (at baseline), Gender(male/female), Disease Duration, Total lesion volume, Treatment at end of study (yes/no), Number of relapses during observation