Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

	Excluded patients (*No.* 610)	Included patients (*No.* 3,198)	*p*
Females, *No. (%)*	417 (68%)	2215 (69%)	*0.667*[a]
Age at onset (y), *mean±SD*	15.1±2.6	15.2±2.5	*0.182*[b]
Age at diagnosis (y), *mean±SD*	22.6±9.1[c]	22.1±8.7	*0.378*[b]
Time from onset to diagnosis (y), *mean±SD*	7.4±8.9[c]	6.9±8.5	*0.713*[d]
Polyfocal onset, *No. (%)*	66 (11%)	370 (12%)	*0.628*[a]
ARR in first year from onset, *mean±SD*	**1.14±0.46**	**1.31±0.67**	***<0.001***[d]
ARR in first 3 years from onset, *mean±SD*	**0.48±0.36**	**0.60±0.46**	***<0.001***[d]
Patients treated with any DMTs, ***No.*** *(%)*	**348 (57%)**	**2913 (91%)**	***<0.001***[a]
Diagnosis epochs, *No. (%)*			***0.020***[a]
<1993	***114 (25%)***[c]	***619 (19%)***	\
1993-1999	***92 (21%)***[c]	***785 (25%)***	\
2000-2006	***134 (29%)***[c]	***934 (29%)***	\
2007-2013	***116 (25%)***[c]	***860 (27%)***	\

eTable 1: Comparison of included versus excluded patients due to missing values.

Are shown demographic, clinical characteristics at onset and DMTs use. Baseline EDSS is not showed due to missing values.

Legend: No., number of patients; y, years; SD, standard deviation; ARR, annualized relapse rate.

[c]*Values reported for 456 patients due to missing values. For diagnosis epochs, the percentage is referred to the group of belonging (e.g. for <1993 is 114/456 for excluded patients and 619/3,198 for included cohort).*

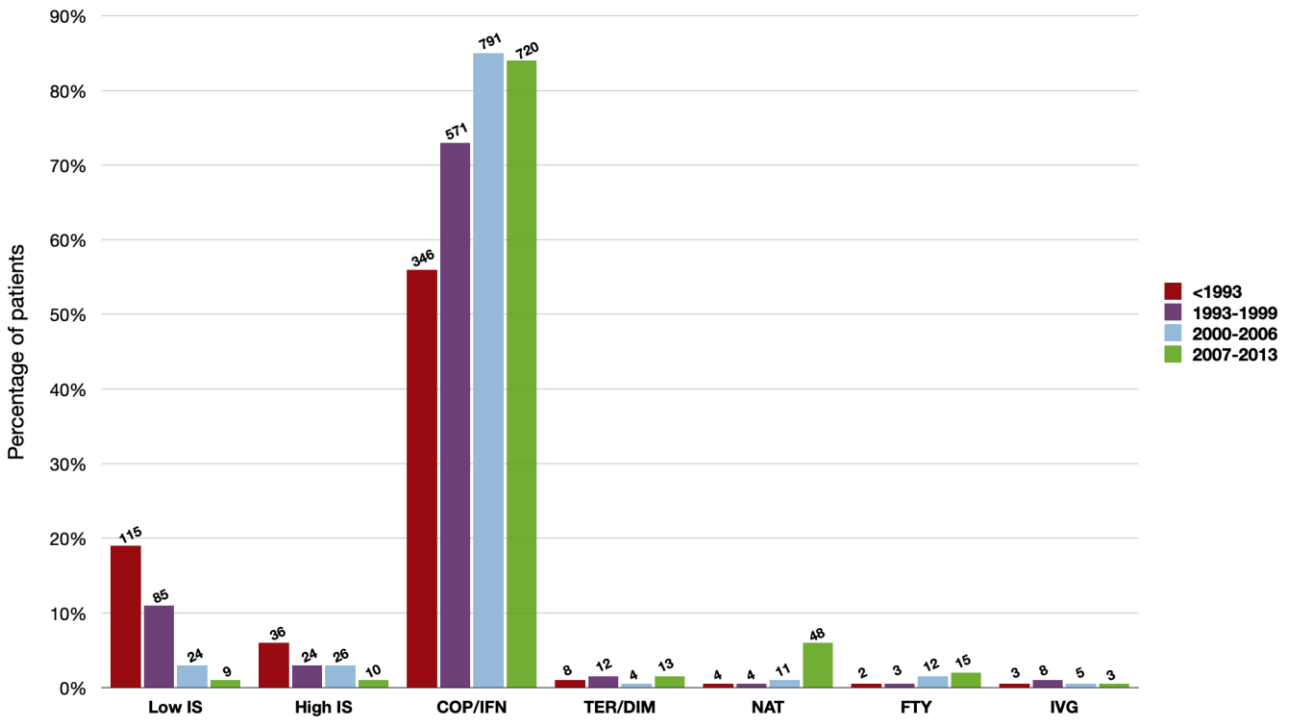
[a]*Chi-square test;* [b]*Student's t-test;* [d]*Mann-Whitney U test*

	Time to reach EDSS ≥4				Time to reach EDSS ≥6			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (CI 95%)	*p*	*HR (CI 95%)*	*p*	*HR (CI 95%)*	*p*	*HR (CI 95%)*	*p*
Diagnosis epoch								
<1993	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
1993-1999	1.03 (0.89-1.20)	0.672	**0.70 (0.58-0.83)**	***<0,001***	1.01 (0.83-1.21)	0.938	**0.72 (0.57-0.90)**	***0.004***
2000-2006	**0.79 (0.67-0.94)**	**0.007**	**0.48 (0.38-0.60)**	***<0.001***	**0.69 (0.56-0.87)**	**0.001**	**0.44 (0.33-0.60)**	***<0.001***
2007-2013	**0.81 (0.65-1.00)**	**0.052**	**0.44 (0.32-0.59)**	***<0.001***	**0.52 (0.38-0.73)**	**<0.001**	**0.30 (0.20-0.46)**	***<0.001***
EDSS score evaluations per year	**1.02 (1.00-1.05)**	**0.039**	1.02 (0.99-1.04)	*0.184*	1.01 (0.98-1.05)	0.488	0.99 (0.96-1.04)	*0.941*
Disease duration at first EDSS evaluation (y)	**0.96 (0.95-0.96)**	**<0.001**	**0.91 (0.89-0.91)**	***<0.001***	**0.96 (0.95-0.97)**	**<0.001**	**0.89 (0.88-0.91)**	***<0.001***
Period of EDSS assessment (y)	**1.01 (1.00-1.02)**	**0.021**	**0.91 (0.89-0.92)**	***<0.001***	1.01 (0.99-1.02)	0.079	**0.90 (0.88-0.92)**	***<0.001***
Age at onset (y)	**1.03 (1.01-1.06)**	**0.007**	1.01 (0.99-1.04)	*0.294*	**1.04 (1.01-1.08)**	**0.006**	1.02 (0.99-1.05)	*0.280*
ARR first 3 years from onset	**1.66 (1.45-1.89)**	**<0.001**	1.12 (0.96-1.30)	*0.144*	**1.47 (1.22-1.78)**	**<0.001**	0.96 (0.78-1.20)	*0.742*
Time from onset to diagnosis (y)	**0.96 (0.95-0.97)**	**<0.001**	1.00 (0.99-1.01)	*0.247*	**0.96 (0.95-0.97)**	**<0.001**	1.00 (0.99-1.02)	*0.428*
Polyfocal onset	1.09 (0.90-1.31)	0.385	0.97 (0.80-1.18)	*0.756*	1.19 (0.93-1.51)	0.160	1.08 (0.85-1.38)	*0.514*
Sex (Male)	**1.24 (1.09-1.41)**	**0.001**	**1.16 (1.02-1.32)**	***0.024***	**1.22 (1.03-1.44)**	**0.021**	1.13 (0.95-1.33)	*0.167*

eTable 2: Univariate and multivariate Cox proportional hazard models of time to reach disability milestones (whole cohort).

Are shown hazard ratios (HR), with their respective 95% confidence interval (CI) and p-values. In bold are indicated statistically significant HR.

Legend: No., number of patients; y, years; ARR, annualized relapse rate.



eFigure 1: Type of the first DMTs received (whole cohort, 3'198 patients).

The first most used DMTs at all time were first-line injectables (COP/IFN), while utilization of low and high potency immunosuppressors gradually decreased over time. Second-line treatments (NAT and FTY) were the most used options after injectables in the latest diagnosis epoch (2007-2013). The changes in first DMTs choice among the four diagnosis epochs were all statistically significant ($p<0.05$, Chi-square test), except for oral first-lines (TER/DIM) and IVG. Above each column is indicated the absolute number of patients receiving the DMTs.

Legend: pts, patients; IS low, low potency immunosuppressors (azathioprine and methotrexate); IS high, high potency immunosuppressors (mitoxantrone and cyclophosphamide); COP, copolymer (glatiramer acetate); IFN, interferons-beta; DIM, dimethyl fumarate; TER, teriflunomide; NAT, natalizumab; FTY, fingolimod; IVG, intravenous immunoglobulin;

Clinical and demographic characteristics	Pediatric-diagnosis (No. 1,300)	Adult-diagnosis (No. 1,898)	*p*
Females, *No. (%)*	876 (67%)	1339 (70%)	*0.061*[a]
Age at onset (y), *mean±SD*	14.4±2.6	15.8±2.2	***<0.001***[b]
Age at diagnosis (y), *mean±SD*	15.5±2.3	26.7±8.5	***<0.001***[b]
Time from onset to diagnosis (y), *median (IQR)*	0.4 (0-1)	8.4 (4-15.5)	***<0.001***[c]
Patients with a polyfocal onset, *No. (%)*	180 (14%)	190 (10%)	***0.001***[a]
ARR in first year, *mean±SD (median)*	1.54±0.84 (1)	1.16±0.48 (1)	***<0.001***[c]
ARR in first 3 years, *mean±SD (median)*	0.75±0.54 (0.7)	0.50±0.35 (0.3)	***<0.001***[c]
EDSS score at diagnosis[d]**,** *median (IQR)*	1.0 (1.0-2.0)	1.5 (1.0-2.5)	***<0.001***[c]
Disease duration at first EDSS evaluation (y), *median (IQR)*	3.2 (0.5-10.5)	14.1 (6-23)	***<0.001***[c]
EDSS score evaluations per year, *median (IQR)*	2.1 (1-3.5)	1.9 (1-3)	***<0.001***[c]
Period of EDSS assessment (y), *median (IQR)*	7.9 (4-13)	8.8 (4-15)	***0.005***[c]
Patients treated with any DMTs, *No. (%)*	1188 (91%)	1641 (86%)	***<0.001***[a]
Age at first DMT (y), *mean±SD*	19.5±6.8	30.0±9.9	***<0.001***[b]
Patients starting DMTs in pediatric age, *No. (%)*	685 (53%)	18 (1%)	***<0.001***[a]
Percentage of time spent on DMTs (%), *median (IQR)*	71% (45-86)	39% (20-57)	***<0.001***[c]
EDSS at first DMT[e]**,** *median (IQR)*	1.5 (1.0-2.0)	2.0 (1.0-3.0)	***<0.001***[c]
Patients treated with high efficacy DMTs, *No. (%)*	634 (49%)	652 (34%)	***<0.001***[a]
Age at first high efficacy DMT (y), *mean±SD*	23.8±7.1	33.6±9.3	***<0.001***[b]
Percentage of time spent on high efficacy DMTs (%), *median (IQR)*	31% (14-49)	15% (7-28)	***<0.001***[c]

eTable 3: Clinical and demographic characteristics of POMS patients with pediatric-diagnosis versus POMS patients with adult-diagnosis.

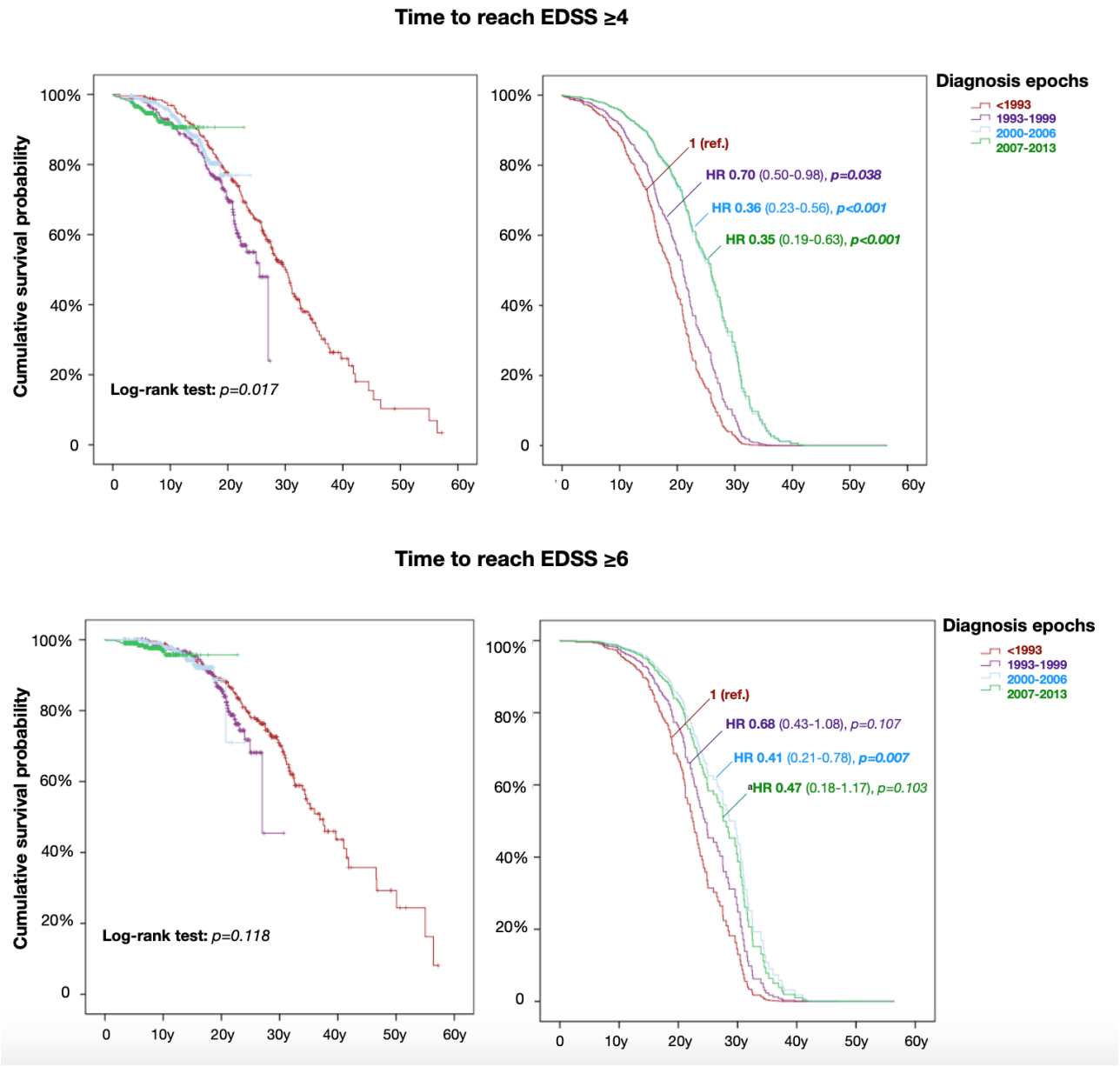
The percentage of time spent on DMTs is ([total time on DMTs/disease duration at last follow-up] x 100).

Legend: No., number of patients; y, years; SD, standard deviation; IQR, inter-quartile range; ARR, annualized relapse rate; DMTs, disease modifying therapies;

[a]*Chi-square test;* [b]*Student's t-test;* [c]*Mann-Whitney test*

[d]*EDSS score evaluated ±6 months from diagnosis (data available on 1342 patients).*

[e]*EDSS score evaluated ±3 months from DMTs initiation (data available on 1728 patients).*



eFigure 2: Time to reach disability milestones compared by diagnosis epochs (pediatric-diagnosis subgroup, 1,300 patients).

On the left are shown Kaplan Meier survival plots stratified by diagnosis epochs. Number of total events (i.e. patients who reached the EDSS milestone) was 303 (23%) for EDSS ≥4 and 165 (13%) for EDSS ≥6.

On the right are shown the survival plots derived from the multivariable Cox proportional-hazards models (adjusted for EDSS score evaluations per year, period of EDSS assessment, disease duration at first EDSS evaluation, age at onset, sex, ARR in the first three years, type of clinical onset, time from onset to diagnosis) with hazard ratios (HR) and 95% confidence interval. Diagnosis epoch <1993 was taken as reference.

[a]*Diagnosis epoch 2007-2013 had a very low number of events (only 10 patients reaching EDSS ≥6, 2% of total), resulting in a high probability of beta-error (i.e. low power).*

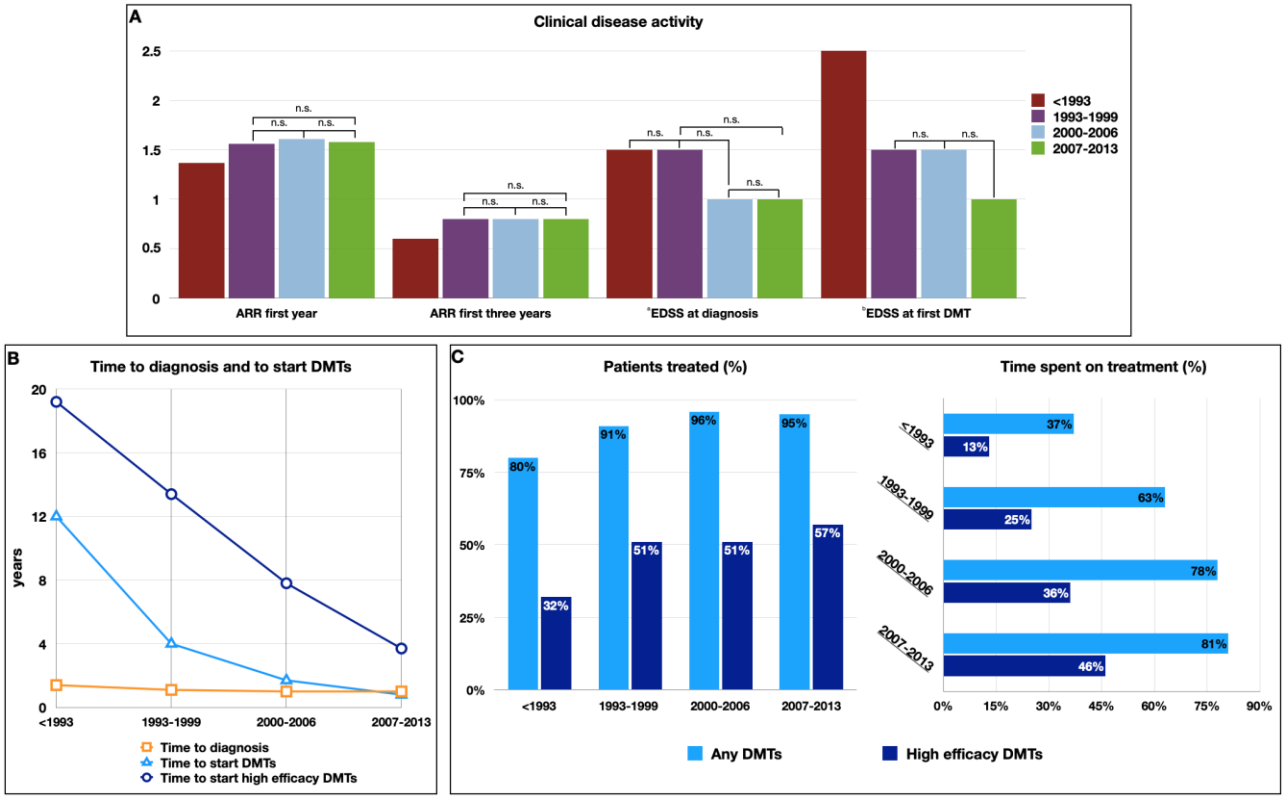
Legend: y, years; ref., reference

	Time to reach EDSS ≥4				Time to reach EDSS ≥6			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (CI 95%)	*p*	*HR (CI 95%)*	*p*	*HR (CI 95%)*	*p*	*HR (CI 95%)*	*p*
Diagnosis epoch								
<1993	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
1993-1999	**1.53 (1.13-2.09)**	***0.007***	**0.70 (0.50-0.98)**	***0.038***	1.47 (0.97-2.24)	*0.072*	0.68 (0.43-1.08)	*0.107*
2000-2006	1.20 (0.81-1.78)	*0.361*	**0.36 (0.23-0.56)**	***<0.001***	1.32 (0.74-2.36)	*0.349*	**0.41 (0.21-0.78)**	***0.007***
2007-2013	**1.79 (1.09-2.92)**	***0.020***	**0.35 (0.19-0.63)**	***<0.001***	**2.29 (1.04-5.09)**	***0.041***	0.47 (0.18-1.17)	*0.103*
EDSS score evaluations per year	1.04 (0.99-1.08)	*0.094*	1.01 (0.96-1.06)	*0.681*	1.03 (0.96-1.10)	*0.403*	0.97 (0.90-1.06)	*0.527*
Disease duration at first EDSS evaluation (y)	**0.97 (0.96-0.98)**	***<0.001***	**0.90 (0.88-0.92)**	***<0.001***	**0.98 (0.96-0.99)**	***<0.001***	**0.90 (0.87-0.93)**	***<0.001***
Period of EDSS assessment (y)	0.99 (0.98-1.01)	*0.396*	**0.91 (0.88-0.93)**	***<0.001***	0.99 (0.97-1.01)	*0.218*	**0.89 (0.85-0.93)**	***<0.001***
Age at onset (y)	1.02 (0.98-1.07)	*0.235*	0.99 (0.94-1.04)	*0.730*	1.03 (0.98-1.09)	*0.241*	1.00 (0.94-1.08)	*0.846*
ARR first 3 years from onset	**1.30 (1.06-1.60)**	***0.011***	1.12 (0.89-1.41)	*0.317*	1.19 (0.90-1.60)	*0.223*	1.04 (0.76-1.44)	*0.789*
Time onset to diagnosis (y)	0.97 (0.91-1.03)	*0.306*	1.00 (0.92-1.08)	*0.987*	0.96 (0.89-1.05)	*0.388*	1.00 (0.89-1.11)	*0.998*
Polyfocal onset	0.93 (0.67-1.28)	*0.655*	0.98 (0.71-1.36)	*0.896*	1.12 (0.74-1.69)	*0.582*	1.27 (0.83-1.91)	*0.276*
Sex (Male)	0.98 (0.77-1.25)	*0.898*	0.98 (0.77-1.25)	*0.882*	0.91 (0.66-1.26)	*0.579*	0.93 (0.66-1.29)	*0.648*

eTable 4: Univariate and multivariate Cox proportional hazard models of time to reach disability milestones (pediatric-diagnosis subgroup).

Are shown the hazard ratios (HR) with their respective 95% confidence interval (CI) and p-values. In bold are indicated statistically significant HR.

Legend: No., number of patients; y, years; ARR, annualized relapse rate.



eFigure 3: Clinical disease activity at onset, time to diagnosis and DMTs management, compared by diagnosis epochs (pediatric-diagnosis subgroup, 1,300 patients).

ARR is expressed as means, number of patients treated as percentage, all the other variables as medians (including the percentage of time spent on treatment, that is ([total time on DMTs/disease duration at last follow-up] x 100).

For all the variables reported in the figure, statistical tests used to evaluate the variation among the four diagnosis epochs (Chi-square, ANOVA or Kruskal-Wallis test) gave significant results (p-values <0.05), except for time to diagnosis (box B, p=0.069). Post-hoc tests for multiple comparisons (six for each variable: Chi-square, Mann-Whitney or t student test, corrected by Bonferroni) were all significant (p<0.05), except for the percentage of patients treated with high efficacy DMTs in 2000-2006 Vs 1993-1999 and the comparisons reported as not significant (n.s.) in box A.

[a]EDSS score evaluated ±6 months from diagnosis, data available on 22 patients (<1993), 79 patients (1993-1999), 174 patients (2000-2006) and 251 patients (2007-2013).

[b]EDSS score evaluated ±3 months from DMT initiation, data available on 94 patients (<1993), 123 patients (1993-1999), 222 patients (2000-2006) and 261 patients (2007-2013).