Big Multiple Sclerosis Data Network: impact of early treatment on long term disability accumulation in relapsing remitting multiple sclerosis patients

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Introduction

- Results from different randomized clinical trials support the beneficial effect of early treatment for multiple sclerosis (MS). To date no real-life data has been provided to support the very long-term impact of such treatment strategy.
- The Danish, Italian and Swedish national MS registries, the MSBase and the OFSEP of France merged data for specific projects in the Big Multiple Sclerosis Data (BMSD) Network.

Objectives

- To evaluate the impact of the time interval from disease onset to the first administration of a disease modifying therapy (DMT) on the long term disability accumulation in a large cohort of relapsing-remitting MS (RRMS) patients collected through the BMSD network.

Methods - Cohort Selection

A cohort of RRMS patients was selected using the following criteria in each of the 5 registries belonging to the BMSD network:

- ≥ 10 years of follow-up (from the 1st to the last recorded visit);
- ≥ 3 Expanded Disability Status Scale (EDSS) score evaluations;
- ≥ 3 years of cumulative DMT exposure.

Methods - Statistical Analysis

EDSS progression definition:

- A minimum of 1 point EDSS increase if the baseline value was between 1 and 5.5, or 1.5-point increase if the baseline EDSS score was 0, and 0.5-point increase if the baseline EDSS score was equal to or above 6.0. A confirmation at repeated assessment at 3 and 12 months later was required to confirm the worsening of EDSS score.

Statistical Analysis

- Cox proportional hazards regression models were used to assess risks of EDSS progression confirmed at 3 and at 12 months and of reaching EDSS 4.0 and EDSS 6.0.
- The following covariates were included in the models:
  - Demographics (age at onset; sex)
  - Baseline EDSS
  - Number of relapses before DMT start
  - Number of relapses after DMT start (included as time-dependent covariate)
  - Time from disease onset to the first DMT start (included as quintiles)
  - Number of EDSS evaluations performed during the follow-up
- Curves of probabilities of reaching an irreversible EDSS 4.0, 6.0 and 1 point EDSS progression confirmed at 3-12 months, stratified by the quintiles of time from disease onset to the first DMT start, were generated from multivariate adjusted Cox models.

Results

- The main clinical and demographic characteristics of the selected cohort (n = 11,934) are reported in **table 1**.
- The time interval between disease onset and the first DMT administration is reported in **table 1**. The 1st quintile of time from disease onset to DMT start included patients treated within 1 year from MS onset (0.6 –[0.4 - 0.9] years).
- During the follow-up irreversible EDSS scores of 4.0 and 6.0 were reached by 3,886 (37.43%) and 2,277 (19.6%) patients, respectively; an EDSS progression event confirmed at 3 and 12 months was reached by 7,098 (59.5%) and 4,159 (34.9%) patients, respectively.
- The multivariate models for the risk of attaining irreversible EDSS scores of 4.0 and 6.0 and the 1-point EDSS progression confirmed at 3 and 12 months, all revealed a significant association with the time to first DMT start (**Table 2**).
- Patients belonging to the 2nd, 3rd, 4th and 5th quintiles of time from disease onset to the first DMT start were all at higher risk of developing irreversible disability and confirmed EDSS progression in comparison to patients belonging to the 1st quintile. Moreover for all the outcome measures the female sex and a lower age at onset were protective factors against disability accumulation, whereas persistent clinical disease activity after the start of DMT was a significant risk factor (**Table 2**).
- Curves generated from multivariate adjusted Cox models .for the probabilities of reaching an irreversible EDSS 4.0, 6.0 and 1 point EDSS progression at 3 and 12 months confirmed are reported in **Fig. 1 A-D.**

Table 1. Clinical and demographic characteristics.

Variable		Value
Patients distribution by source registry, n (%)		
	Italian MS Registry	4,921 (41.23)
	Danish MS Registry	1,530 (12.82)
	Swedish MS Registry	1,194 (10.01)
	OFSEP	1,744 (14.61)
	MSBase	2,545 (21.33)
Female sex, n (%)		8,452 (71.04)
Classes of age at onset, years, n (%)		
	≤12	97 (0.82)
	>12 - ≤15	288 (2.42)
	>15 - ≤18	739 (6.21)
	>18 - ≤25	3,425 (28.79)
	>25 - ≤30	2,581 (21.69)
	>30 - ≤45	4,180 (35.13)
	>45	588 (4.94)
Age at Onset, years, Median (IQR)		27.70 (22.30 - 34.60)
N. of relapses prior to DMT start, Median (IQR)		2.00 (1.00 - 4.00)
Baseline EDSS score, Median (IQR)		2.00 (1.00 - 3.00)
First DMT prescription, n (%)		
	I line	11,802 (98.9%)
	II line	132 (1.1%)
N. of relapses after DMT start, Median (IQR)		3.00 (1.00 - 6.00)
Follow-up duration, years, Median (IQR)		13.20 (11.40 - 15.40)
N. of EDSS recorded per patient, Median (IQR)		21.00 (14.00 - 32.00)
Cumulative DMT exposure, years, Median (IQR)		10.5 (6.9 – 13.1)
Quintiles of time from disease onset to the first DMT start, years, Median (IQR)		
	Q1	0.6 (0.4 – 0.9)
	Q2	1.8 (1.5 – 2.2)
	Q3	3.8 (3.2 – 4.5)
	Q4	7.3 (6.2 – 8.5)
	Q5	14.6 (11.9 – 18.5)

Table 2. Multivariate Cox models for the risk of attaining irreversible EDSS 4.0, 6.0 and 1 point EDSS progression confirmed at 3 and 12 months.

	EDSS 4.0		EDSS 6.0		EDSS progression confirmed at 3 months		EDSS progression confirmed at 12 months	
	HR 95 % CI	p	HR 95 % CI	p	HR 95 % CI	p	HR 95 % CI	p
Sex								
Female	0.88 (0.82-0.94)	.0003	0.75 (0.69-0.82)	<.0001	0.92 (0.87-0.96)	.0009	0.87 (0.81-0.93)	<.0001
Male [reference category]								
Classes of age at onset								
≤12	0.56 (0.38-0.84)	.004	0.52 (0.28-0.99)	.05	0.54 (0.39-0.73)	<.0001	0.71 (0.47-1.07)	.10
>12 - ≤15	0.52 (0.39-0.69)	<.0001	0.69 (0.49-0.97)	.04	0.67 (0.55-0.82)	.0001	0.89 (0.69-1.16)	.40
>15 - ≤18	0.65 (0.53-0.80)	<.0001	0.63 (0.49-0.83)	.0007	0.72 (0.61-0.84)	<.0001	0.90 (0.74-1.10)	.31
>18 - ≤25	0.60 (0.51-0.70)	<.0001	0.64 (0.52-0.78)	<.0001	0.66 (0.58-0.75)	<.0001	0.78 (0.67-0.91)	.002
>25 - ≤30	0.58 (0.49-0.67)	<.0001	0.67 (0.55-0.82)	<.0001	0.68 (0.60-0.76)	<.0001	0.75 (0.65-0.88)	.0002
>30 - ≤45	0.76 (0.66-0.88)	.0002	0.83 (0.69-0.99)	.04	0.83 (0.75-0.93)	.001	0.85 (0.74-0.97)	.02
>45 [reference category]								
Quintiles of time to 1st DMT start								
Q5	1.92 (1.70-2.17)	<.0001	1.88 (1.59-2.21)	<.0001	1.76 (1.61-1.93)	<.0001	1.61 (1.43-1.81)	<.0001
Q4	1.51 (1.35-1.69)	<.0001	1.66 (1.42-1.93)	<.0001	1.48 (1.36-1.61)	<.0001	1.37 (1.23-1.53)	<.0001
Q3	1.34 (1.20-1.50)	<.0001	1.39 (1.19-1.62)	<.0001	1.36 (1.26-1.47)	<.0001	1.36 (1.22-1.51)	<.0001
Q2	1.21 (1.09-1.35)	.0005	1.11 (0.94-1.30)	.22	1.21 (1.12-1.31)	<.0001	1.23 (1.11-1.36)	.0001
Q1 [reference category]								
N. of relapses prior to DMT start								
1	1.00 (0.94-1.07)	0.94	1.00 (0.91-1.09)	.93	1.16 (1.10-1.22)	<.0001	1.01 (0.94-1.08)	.80
> 1 [reference category]								
Decade of birth	0.83 (0.76-0.90)	<.0001	0.76 (0.67-0.85)	<.0001	0.90 (0.85-0.96)	.0007	0.73 (0.68-0.80)	<.0001
N. of EDSS recorded per patient	1.01 (1.01-1.01)	<.0001	1.00 (1.00-1.00)	.07	1.00 (1.00-1.01)	<.0001	0.97 (0.97-0.97)	<.0001
N. of relapses after DMT start	3.36 (3.06-3.69)	<.0001	2.52 (2.23-2.86)	<.0001	2.52 (2.38-2.68)	<.0001	2.37 (2.19-2.57)	<.0001
Baseline EDSS score	1.82 (1.75-1.89)	<.0001	1.77 (1.72-1.83)	<.0001				

Figure 1. Curves generated from multivariate adjusted Cox models for the probabilities of reaching an irreversible EDSS 4.0 (A), 6.0 (B) and 1 point EDSS progression confirmed at 3-12 months (C, D) by each quintile of time from disease onset to DMT start.

Fig. 1A

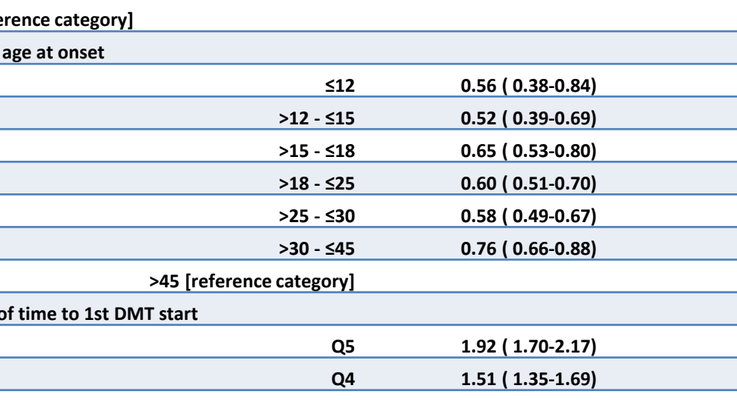


Fig. 1B

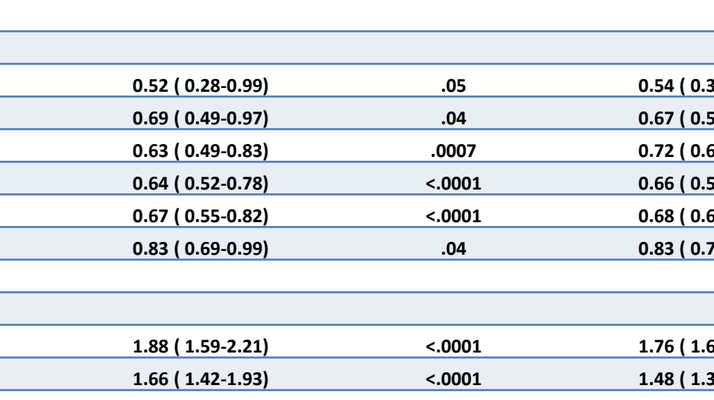


Fig. 1C

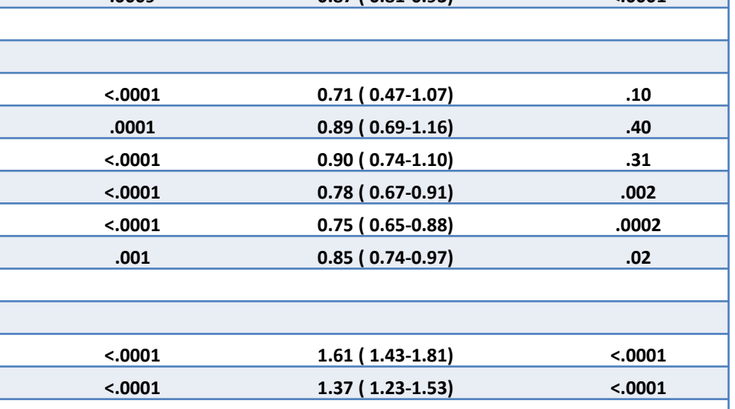
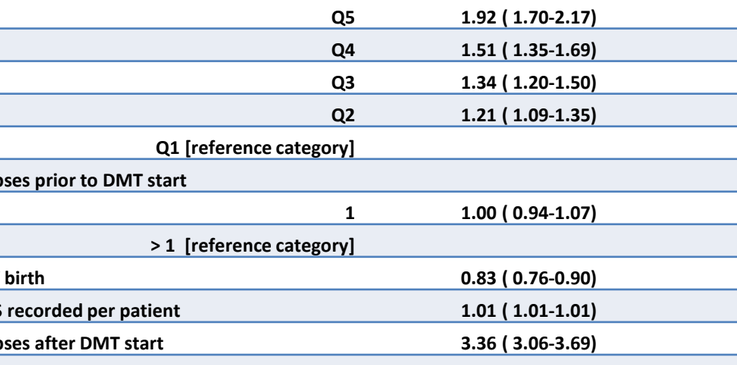


Fig. 1D



Figures legend:
Q1-5: Quintiles of time from disease onset to the first DMT start, years, Median (IQR)

Q1 = 0.6 (0.4 – 0.9)
Q2 = 1.8 (1.5 – 2.2)
Q3 = 3.8 (3.2 – 4.5)
Q4 = 7.3 (6.2 – 8.5)
Q5 = 14.6 (11.9 – 18.5)

Conclusions

Real-world data from the BMSD network allows to confirm, in a very large population of RRMS patients followed-up for at least 10 years, greater beneficial effects of early treatment strategy in delaying the accumulation of irreversible disability. We are evaluating advanced statistical approaches to overcome potential bias that could affect the results.

Acknowledgements and Disclosures: This project was supported by Biogen International (Zug, Switzerland).

Pietro Iaffaldano has served on scientific advisory boards for Biogen Idec and Novartis, and has received funding for travel and/or speaker honoraria from Genzyme, Biogen Idec, Merck-serono, Teva and Novartis.
Helmut Butzkueven reports Research support from Biogen, Novartis, Merck. Advisory Board and Speaker fees from Roche, Biogen, Novartis, Merck, Teva, Medscape, Oxford Pharmagenesis
Jan Hillert has received honoraria for serving on advisory boards for Biogen, Sanofi-Genzyme and Novartis and speaker's fees from Biogen, Novartis, Merck-Serono, Bayer-Schering, Teva and Sanofi-Genzyme. He has served as P.I. for projects, or received unrestricted research support from, BiogenIdec, Merck-Serono, TEVA, Sanofi-Genzyme and Bayer-Schering. His MS research is funded by the Swedish Research Council and the Swedish Brain foundation.
Melinda Magyari has served on scientific advisory board for Biogen Idec and Novartis, Merck, Sanofi, has received honoraria for lecturing from Biogen Idec, Merck, Novartis, Genzyme, has received support for congress participation from Biogen Idec, Novartis, Genzyme, Teva.
Maria Trojano has received honoraria for consultancy or speaking from Biogen, Sanofi-Aventis, Merck Serono and Bayer-Schering and research grants from Merck Serono, Biogen and Novartis.
Sandra Vukusic has received consultancy fees, speaker fees, research grants (non-personal) or honoraria from Biogen, Geneuro, Genzyme-Sanofi, Medday, Merck-Serono, Novartis, Roche and Teva.