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 MS registers, the MSBase and the OFSEP of France merged data for specific projects in the Big Multiple Sclerosis Data Network (BMSD) model.

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:

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

Results

- The main clinical and demographic characteristics of the selected cohort (n = 11,934) are reported in Table 1.
- The time interval from disease onset to 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 (0.6–0.9 years).
- During the follow-up irreversible EDSS scores of 4.0 and 6.0 were reached by 3,886 (37.4%) and 2,277 (21.9%) patients, respectively; an EDSS progression event confirmed at 3 and 12 months was reached by 7,098 (95.9%) 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 achieving 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 in Fig. 1A-D.

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 ≥ 6.0 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.

Table 1. Clinical and demographic characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (IQR)</th>
<th>HR 95% CI</th>
<th>p</th>
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<tbody>
<tr>
<td>Sex</td>
<td>Female: 0.81 (0.80-0.94)</td>
<td>0.75 (0.81-0.87)</td>
<td>&lt;0.001</td>
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<td>Male: 0.71 (0.69-0.74)</td>
<td>0.45 (0.42-0.49)</td>
<td>&lt;0.001</td>
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<tr>
<td>Q1</td>
<td>7.00 (6.00-8.00)</td>
<td>1.01 (1.00-1.03)</td>
<td>&lt;0.001</td>
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<td>1.30 (1.20-1.40)</td>
<td>0.73 (0.69-0.78)</td>
<td>&lt;0.001</td>
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<td>1.62 (1.50-1.75)</td>
<td>0.78 (0.74-0.82)</td>
<td>&lt;0.001</td>
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<tr>
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<td>1.88 (1.75-2.00)</td>
<td>0.75 (0.70-0.81)</td>
<td>&lt;0.001</td>
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<td>2.10 (2.00-2.20)</td>
<td>0.77 (0.73-0.80)</td>
<td>&lt;0.001</td>
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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.

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.

References


Figures

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