Beyond pivotal trials inclusion criteria: real world clinical profile of multiple sclerosis patients under disease modifying treatment in Argentina.


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Conflicts of interest

- The authors do not have any potential financial conflict of interest relating to this poster.
- Unrestrictive research grants from Biogen Argentina, Genzyme Argentina, Merck Argentina, Novartis Argentina and Roche Argentina allowed the development and implementation of the Registry (RelevarEM). Those grants did not interfere in the development plan, variables, PI selection, patient information nor other aspects of the Registry.
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Background and objective

• Background: In multiple sclerosis (MS), randomized controlled trials (RCT) have provided relevant information about the efficacy and safety in ideal scenarios. While RCT are powerful tools for developing scientific evidence based on their high internal validity, there is always uncertainty about the generalizability, especially since the populations enrolled in such studies may differ in significant ways from those seen in clinical practice.

• Objective: to describe the frequency and clinical profile of MS patients under disease modifying treatment (DMT) in Argentina that would have not fulfilled inclusion criteria in RCT.
### Pivotal clinical trials for approved DMT in RRMS in Argentina.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pivotal trial</th>
<th>Age inclusion criterion (in years)</th>
<th>EDSS inclusion criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>βInterferon 1b</td>
<td>IFNB MS Group (1993)</td>
<td>18 – 50</td>
<td>0 – 5.5</td>
</tr>
<tr>
<td>βInterferon 1a IM</td>
<td>MSCRG (1996)</td>
<td>18 – 55</td>
<td>1 – 3.5</td>
</tr>
<tr>
<td>βInterferon 1a SC</td>
<td>PRISMS (1998)</td>
<td>All adults</td>
<td>0 – 5.0</td>
</tr>
<tr>
<td>Glatiramer Acetate</td>
<td>Copolymer 1 Multiple Sclerosis Study Group (1995)</td>
<td>18 – 45</td>
<td>0 – 5.0</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>AFFIRM (2006)</td>
<td>18 – 50</td>
<td>0 – 5.0</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>FREEDOMS (2010)</td>
<td>18 – 55</td>
<td>0 – 5.5</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>TEMSO (2011)</td>
<td>18 – 55</td>
<td>0 – 5.5</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>DEFINE (2012)</td>
<td>18 – 55</td>
<td>0 – 5.0</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>CARE MS1 (2012)</td>
<td>18 – 50</td>
<td>0 – 5.0</td>
</tr>
<tr>
<td></td>
<td>CARE MS2 (2012)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>OPERA 1 (2017)</td>
<td>18 – 50</td>
<td>0 – 5.5</td>
</tr>
<tr>
<td></td>
<td>OPERA 2 (2017)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Methods**

- MS patients included in the Argentinean MS and NMOSD registry (RelevarEM, NCT 03375177) were analyzed.

- RelevarEM is a longitudinal, strictly observational MS and NMOSD registry in Argentina. From May 2018 to March 2020, the centers and principal investigators were contacted and incorporated into the Registry.

- All patients with definite MS and receiving DMT at 31 December 2019 were screened, those with EDSS ≥6, phenotypes secondary progressive (SP) and primary progressive (PP)(with other DMT than ocrelizumab) and age <18 and >55 years old were included in the analysis. Subjects with radiologically isolated syndrome (N6) were excluded of the analysis.
Results

- 1782 patients with MS receiving DMT were screened.

- 465 (26%) would not have been included in a pivotal trial.

- From the 465, 218 had and EDSS ≥6, 67 had phenotype SP and 19 PP; 292 were patients with <18 and >55 years of age (2 under 18 years old).
### Results

Characteristics of patients under DMT who wouldn’t have been candidates for pivotal clinical trials.

<table>
<thead>
<tr>
<th></th>
<th>Age &lt;18 or &gt;55 y.o. N=292</th>
<th>EDSS ≥6 N= 218</th>
<th>SPMS N= 67</th>
<th>PPMS (except treated with ocrelizumab) N=19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age mean (SD)</strong></td>
<td>&gt;55 y.o: 62 (6,6)</td>
<td>50,3 (11,7)</td>
<td>52 (11,9)</td>
<td>49,9 (9,8)</td>
</tr>
<tr>
<td><strong>Female (%)</strong></td>
<td>196 (67%)</td>
<td>137 (63%)</td>
<td>47 (70%)</td>
<td>7 (37%)</td>
</tr>
<tr>
<td><strong>Phenotype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIS</td>
<td>6</td>
<td>CIS: 1</td>
<td>SPMS 67</td>
<td>PPMS 19</td>
</tr>
<tr>
<td>RRMS</td>
<td>248</td>
<td>RRMS: 148</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPMS</td>
<td>26</td>
<td>SPMS: 53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPMS</td>
<td>12</td>
<td>PPMS: 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EDSS median (IQR)</strong></td>
<td>3,5 (2 – 6)</td>
<td>6,5 (6 – 7)</td>
<td>6 (6 – 7)</td>
<td>6 (3,75 – 6)</td>
</tr>
</tbody>
</table>

DMTs indicated according to exclusion criteria.

Most prescribed DMT among patients with:

- Age >55 beta interferon (35%)
- EDSS ≥6 fingolimod (31%)
- Phenotype SPMS fingolimod (30%)
- Phenotype PPMS fingolimod and glatiramer acetate (each 26%)

Limitations

- Real life studies have several limitations (recording bias, accuracy, definition of case) that have to be taken into consideration before arriving to any conclusion.

- One important inclusion criterion in clinical trials, disease activity, was not considered in the analysis because patients have indications to continue under DMT even if not activity of the disease is detected.
Conclusions

- In our registry, we found a significant number of MS patients receiving DMT, who would have not been included in pivotal trials.
- Real life evidence is highly relevant to assess effectiveness as well as safety of DMT in this subset of patients.