RELEVAREM

# 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.


| Drug | Pivotal trial | Age inclusion criterio (in years) | EDSS inclusion criteria |
|---|---|---|---|
| βInterferon1b | IFNB MS Group (1993)[1] | 18 – 50 | 0 – 5.5 |
| βInterferon 1a IM | MSCRG (1996) [2] | 18 – 55 | 1 – 3.5 |
| βInterferon 1a SC | PRISMS (1998) [3] | All adults<br>Median (IQR): 34·9 (29·1–40·4) | 0 – 5.0 |
| Glatiramer Acetate | Copolymer 1 Multiple Sclerosis Study Group (1995) [4] | 18 – 45 | 0 – 5.0 |
| Natalizumab | AFFIRM (2006) [5] | 18 – 50 | 0 – 5.0 |
| Fingolimod | FREEDOMS (2010) [6]<br>TRANSFORMS (2010) | 18 – 55 | 0 – 5.5 |
| Teriflunomide | TEMSO (2011) [7] | 18 – 55 | 0 – 5.5 |
| Dimethyl fumarate | DEFINE (2012) [8]<br>CONFIRM (2012) | 18 – 55 | 0 – 5.0 |
| Alemtuzumab | CARE MS1 (2012) [9]<br>CARE MS2 (2012) | 18 – 50 | 0 – 5.0 |
| Ocrelizumab | OPERA 1 (2017) [10]<br>OPERA 2 (2017) | 18 – 55 | 0 – 5.5 |

1. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. Neurology. 1993;43(4):655-661. 2. Jacobs, L. D., Cookfair, D. L., et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol 1996, 39(3), 285–294. 3. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Lancet. 1998;352(9139):1498-1504. 4. Johnson KP, Brooks BR, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology. 1995;45(7):1268-1276. 5.Polman CH, O'Connor PW, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006;354(9):899-910. 6. Cohen JA, Barkhof F, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):402-415. 7. O'Connor P, Wolinsky JS, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med. 2011;365(14):1293-1303. 8. Gold R, Kappos L, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med. 2012;367(12):1098-1107. 9. Cohen JA, Coles AJ, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012;380(9856):1819-1828. 10. Hauser SL, Bar-Or A, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med. 2017;376(3):221-234.

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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.

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## 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.

| | Age <18 or >55 y.o.<br>N=292 | EDSS ≥6<br>N= 218 | SPMS<br>N= 67 | PPMS (except treated with ocrelizumab)<br>N=19 |
|---|---|---|---|---|
| **Age mean (SD)** | >55 y.o: 62 (6,6) | 50,3 (11,7) | 52 (11,9) | 49,9 (9,8) |
| **Female (%)** | 196 (67%) | 137 (63%) | 47 (70%) | 7 (37%) |
| **Phenotype** | CIS: 6<br>RRMS: 248<br>SPMS: 26<br>PPMS: 12 | CIS: 1<br>RRMS: 148<br>SPMS: 53<br>PPMS: 16 | SPMS 67 | PPMS 19 |
| **EDSS median (IQR)** | 3,5 (2 – 6) | 6,5 (6 – 7) | 6 (6 – 7) | 6 (3,75 – 6) |

SD: standard deviation, IQR: interquartile range, CIS: clinically isolated syndrome, RRMS: relapsing remitting multiple sclerosis, SPMS: secondary progressive multiple sclerosis, PPMS: primary progressive multiple sclerosis.

# Results

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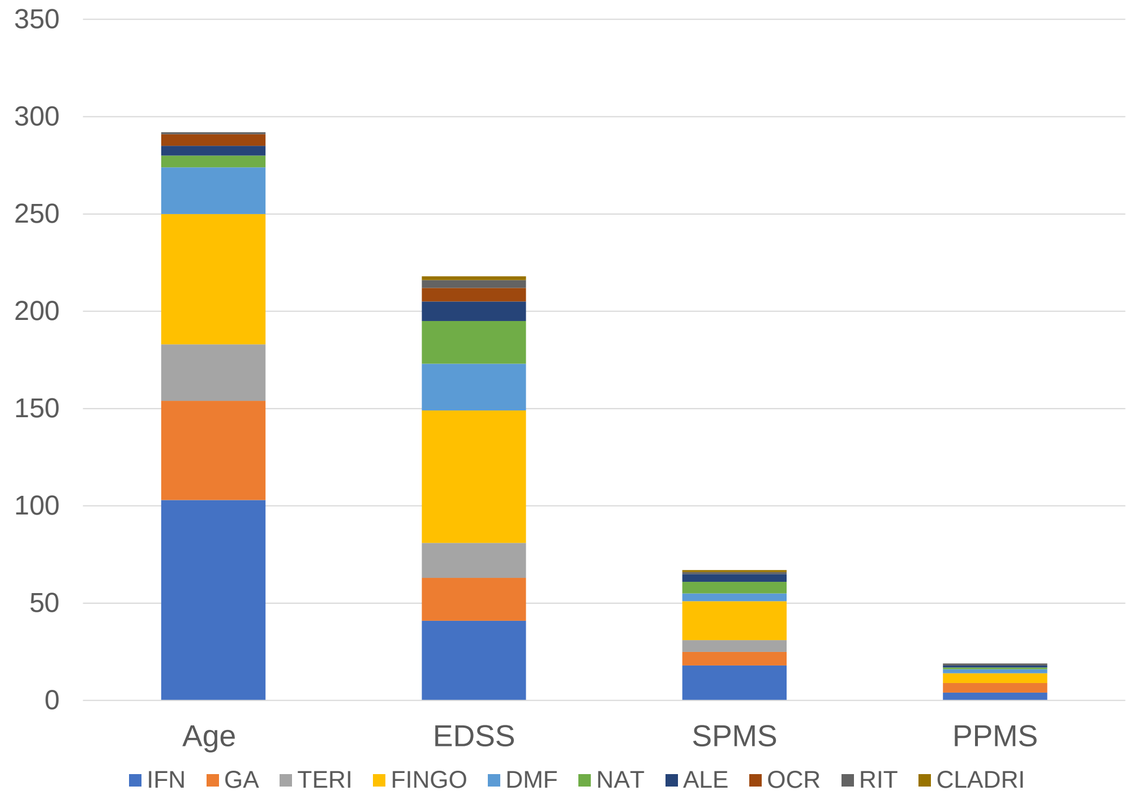
DMTs indicated according to exclusion criteria.




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%)

DMT: disease modifying therapy, SPMS: secondary progressive multiple sclerosis, PPMS: primary progressive multiple sclerosis, IFN: beta interferón, GA: glatiramer acetate, TERI: teriflunomide, FINGO: fingolimod, DMF: dimethyl fumarate, NAT: natalizumab, ALE: alemtuzumab, OCR: ocrelizumab, RIT: rituximab, CLADRI: cladribine.


## 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 con 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.