Long-term follow up of an Italian cohort of pediatric Multiple Sclerosis patients: real world data from San Raffaele Hospital

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Introduction and Purpose

Multiple Sclerosis (MS) onset during childhood or adolescence occurs in 3%-10% of cases [1]. Most of disease modifying treatments (DMTs) available for MS have not been tested in this specific population and data about the use of these medications in pediatric-MS (ped-MS) are scarce and mainly derived from observational studies [3]. Currently, very few data are available on long-term follow-up of ped-MS subjects treated with DMTs [4].

The aim of this work is to present baseline characteristics and long-term follow up (FU) of an Italian cohort of ped-MS patients.

Methods

This study is a retrospective evaluation of data prospectively acquired at San Raffaele Hospital MS Center. Data regarding MS onset, annualized relapse rate (ARR), Expanded Disability Status Scale (EDSS) score and treatments were collected from clinical records at our MS Center (*Table 1*). Patients were divided in two different cohorts, basing on MS onset year (MS onset ≤ 2007 and > 2007). Descriptive statistics (mean, standard deviation, etc.) were used for continuous variables, while categorial variables were described as percentage of subjects falling in each group. We compared ARR and EDSS score before and after therapy initiation using Friedman and Wilcoxon tests. Baseline predictors were tested in a multivariate logistic regression model for disability worsening. Among baseline predictors, age of therapy initiation and MS onset were considered as binomial variables (< and ⩾12 years).

	PED- MS patients (144)
SEX Female/Male	101/43
AGE at **ONSET** Mean ± SD	14.56 ± 2.47
AGE at **LAST FOLLOW UP** Mean ± SD	24.89 ± 6.03
ONSET Monofocal/Polifocal	109/35
ARR at **ONSET** Mean ± SD	4.40 ± 4.77
EDSS at **ONSET** Median (range)	1.5 (0-6)
Years of **FOLLOW UP** Mean ± SD	9.40 ± 6.24

Table 1. Clinical and demographic data

Results

TREATMENTS

Whole Cohort

Mean age at therapy initiation was 15.63 ± 2.48 years and median duration of pre treatment phase was 8 months. The majority of subjects were initially treated with interferon-beta (IFN) (59.72%). Induction with immunosuppressants (IS) at onset was performed in 4.86% of cases, while second-line treatments as first therapy were chosen in 18.05% of subjects. Overall, 50.5% of subjects were treated with Natalizumab (NAT), in particular 20 patients (13.89%) as first therapy.

Only 18.10% of patients remained on first treatment, while 81.9% underwent at least one switch: 27.10% performed only 1 switch, while 45.80% and 27.10% performed 2-3 and 4 switches, respectively. The first switch occurred after a mean of 2.90 ±3.17 years and was predominantly to other first line agents, frequentlys high-frequency IFN (30.43%) while only 25.22% switch to second line; subsequent switches were mainly to second-line therapy (*Figure 1*).

MS onset ≤ 2007

Mean age at therapy initiation was 15.75 ± 2.72 years and median duration of pre treatment phase was 13 months. IFN was still the most common drug chosen as first therapy (75.86%) and IS as induction therapy were used at onset in 3.45% of cases. Natalizumab (NAT) as first therapy was chosen in only 1 subject (1.72%; to note NAT was licensed in Italy for adults in 2007) and no other second-line treatments were available at that time (*Figure 2*).

Only 2.34% of patients remained on first treatment. The first switch occurred after a mean of 4.32±3.85 years and was predominantly to second-line therapy (12.50% IS and 8.93% NAT).

MS onset > 2007

Mean age at therapy initiation was 15.51 ± 2.31 years and median duration of pre treatment phase was 8 months. 48.83% of subject were initially treated with IFN, IS as induction therapy at onset was performed in 5.81% of subjects and second-line at onset was chosen in 26.75% of cases. In particular, the second line choice was NAT in 19 patients (22.10%) (*Figure 2*).

27.91% of patients remained on first treatment. The first switch occurred after a mean of 2.89±3.17 years and was predominantly to second-line therapy, specifically the majority switched to NAT.

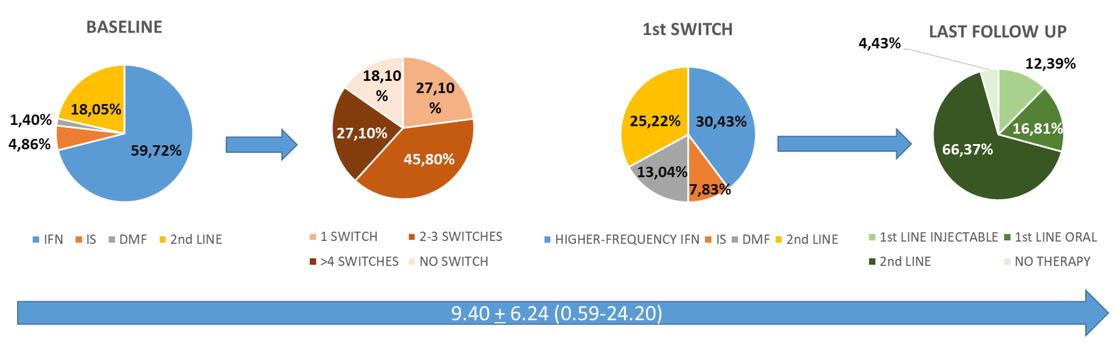

Figure 1. **Treatment history of the whole cohort.** First-line agents include injectable drugs (glatiramer acetate, interferons beta-IFN) and oral drugs (teriflunomide and dimethyl fumarate-DMF). Second-line agents: fingolimod, natalizumab, alemtuzumab, rituximab, ocrelizumab and cladribine. Immunosuppressors (IS) include azathioprine, mitoxantrone and cyclophosphamide

Figure 2. ***DMTs chosen as first treatments in the two different cohorts*** *(IFN: interferon-beta, IS: immunosuppressants, GA: glatiramer acetate, DMF: dimethyl fumarate, FTY: fingolimod, NAT: natalizumab, RTX: rituximab)*

CLINICAL OUTCOMES and BASELINE PREDICTORS OF a WORSE MS COURSE

Considering the whole cohort, compared to pre-treatment phase, ARR was significantly reduced during the first treatment (from 4.40 ± 4.77 to 1.95 ± 2.75) and remained low at last FU (0.03± 0.14), *p<0.001* in both instances. This trend is confirmed and results remain statistically significant also when analyzing patients by the two different cohorts (*Figure 3*).

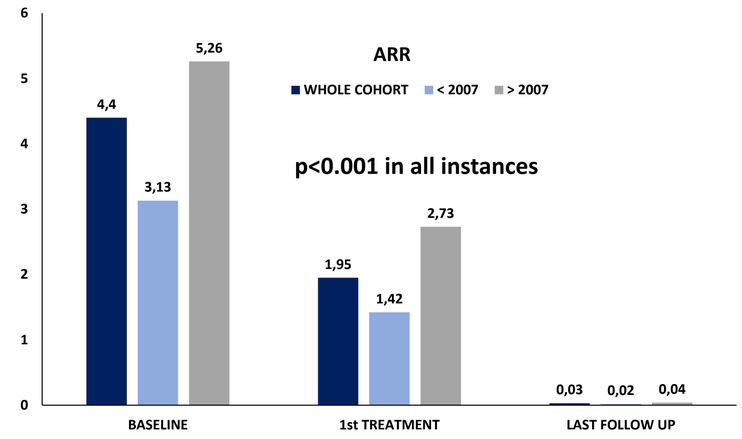

Figure 3. ***Mean ARR at baseline, after the first treatment and at last follow up in the considered cohorts***

As regards EDSS score (mean ± standard deviation), considering all patients, 83% had a stable or improved EDSS score while only 17% had an EDSS score worsened at last follow up (FU) with respect to baseline. Specifically, we found a statistically significant EDSS increase at last FU compared to the end of first treatment (1.55 ± 0.86 to 1.64 ± 1.98, *p=0.05*). Considering MS onset ≤ 2007, we found an EDSS increase from baseline to end of first treatment (1.57 ± 0.89 to 1.61 ± 0.87, *not significant*) more pronounced at last follow up (1.61 ± 0.87 to 2.03 ± 2.98, *not significant*); on the contrary, EDSS increase from onset to last FU was statistically significant, *p<0.05*. Considering MS onset > 2007, we saw a significant EDSS improvement from baseline to end of first treatment (1.71 ± 0.89 to 1.51 ± 0.86, *p=0,02*), confirmed at last FU (1.51 ± 0.86 to 1.41 ± 0.94, *p=0,03*) (*Figure 4*). Overall 76% of our patients had no relapses and no disability progression at last FU, therefore we can consider them as having no evidence of clinical disease activity at last FU.

Finally, considering all patients, we found a trend towards significance in the association between a polyfocal disease onset and risk of disability progression (OR 0.3, p=0.08).

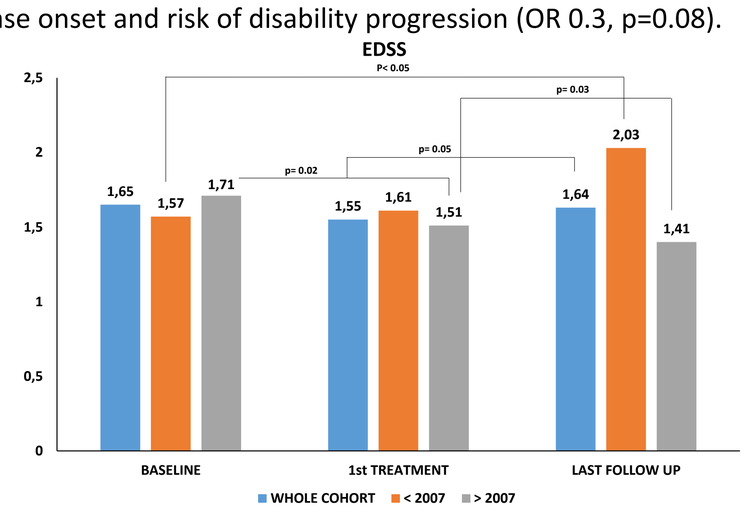

Figure 4. ***Mean EDSS score at baseline, after the first treatment and at last follow up in the considered cohorts***

SAFETY AND ADHERENCE

Considering all patients, 56.52% changed treatment for disease activity. Treatment discontinuation due to clinical side effects was in 16.52% of cases (e.g. headache, flu-like symptoms, persistent fever) and to hematological side effects in 4.35% of cases (e.g increase of liver enzymes, leukopenia). A scheduled stop due to specific treatment strategies occurred in 18.26% of cases and other reasons for treatment discontinuation were pregnancy and patient decision (*Figure 5*).

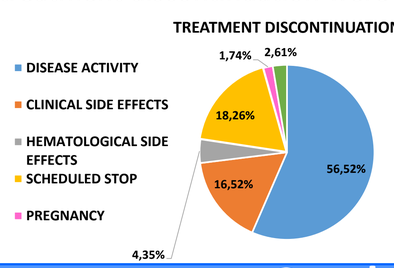

Figure 5. ***Causes of treatment discontinuation***

Conclusions

Ped-MS patients benefited from first-line agents, but the majority had to switch to more powerful DMTs. IFN was the most common DMT chosen as first treatment in both cohorts, but patients with MS onset >2007 were more likely to be treated with second line agents, in particular natalizumab, from the beginning, and to perform an earlier switch to second line therapy. Taken together, those characteristics could influence disability reduction over time. Finally, a polyfocal disease onset seemed to be associated with an increased risk of disability progression. Overall, our findings highlight the importance of a careful treatment selection and accurate clinical FU in ped-MS population. PED-MS is a vulnerable population with a long life expectancy and therefore our goal is to avoid physical but also cognitive disability to ensure a good quality of life.

Bibliography

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