Long-term outcome of pediatric MS patients treated with first-line injectable treatments: a multicentre, retrospective, cohort study.

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Background

- Many disease-modifying therapies (DMT) are currently available for adults with relapsing-remitting multiple sclerosis (RR-MS) but no medication has completed testing for pediatric MS (ped-MS) in randomized placebo-controlled trials. In recent years several pediatric MS trials have been launched;
- The high frequency of relapses in ped-MS, especially in the first years, with a relapse rate higher than that of adults, and the pattern of MRI lesions, with more pronounced inflammatory aspects, support the use of DMT in the pediatric population as they mainly target the inflammatory component;
- Use of DMT in ped-MS remains off-label in many countries, especially for nevertheless they are widely used in the treatment of children and adolescents with RR-MS;
- Several observational studies have provided data on safety and efficacy of Interferon-beta (IFNb) and glatiramer acetate (GA) in the ped-MS population, but data are not available after a long-term follow-up;

Objectives

- In 2009 we reported the results of immunomodulatory treatment in a cohort of 130 ped-MS patients after 4-6 years of follow-up. We describe here the results update to 2016;

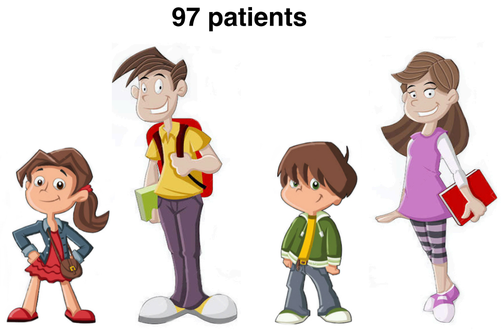
Methods

- **Type of study:** multicenter, observational retrospective;
- **Population included:** all ped-MS patients initiating GA or IFNb included in a previous work of our group and regularly followed for at least 5 years;
- **Data collected:** demographic characteristics, clinical outcomes (including the first events as a relapse) and treatments received;
- **Statistical analysis performed:**
  - Comparison of annualized relapse rate (ARR) and EDSS score before Vs after therapy initiation (Friedman and Wilcoxon tests) in the whole cohort and in two groups divided by type of therapy received during the whole follow-up (first-line and second-line&others therapies);
  - Multivariate analysis to predict the clinical course of MS (measured by 3 endpoints: last EDSS score, ARR during follow-up and EDSS score worsening of ≥ 1 point at last observation) using seven baseline variables (see results for details);
  - Comparison of baseline characteristics and clinical outcomes in patients starting treatment before Vs after 12 years of age using independent sample tests (Chi-square, Spearman rank);

Results

Baseline clinical and demographic characteristics of the whole cohort

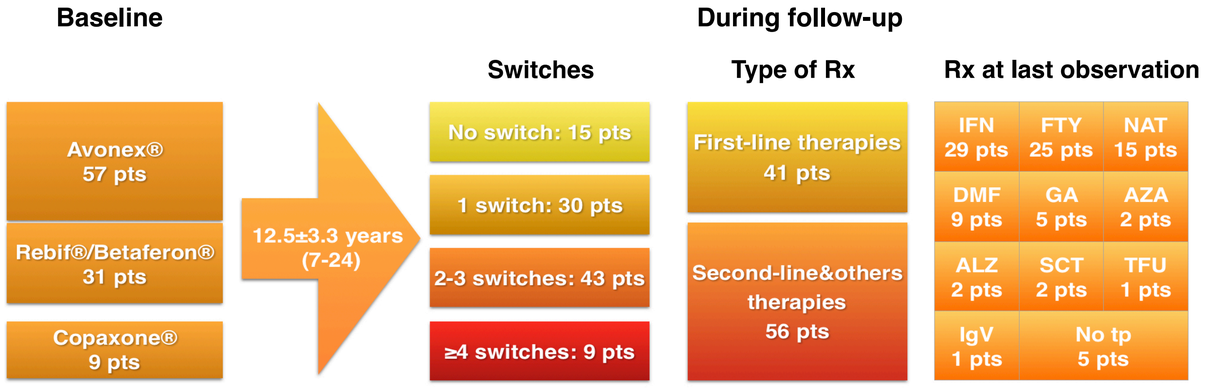
97 patients



Gender (Female/Male)	67/30
Age of MS onset (years)	12.3±2.5 (6-16)
Type of onset (mono/multifocal)	69/28
Disease duration (months)	19.5±21.0 (1-120)
ARR from onset	3.2±2.6 (0.2-12)
EDSS score	1.4±0.8 (0-4.5)
Age of therapy initiation (years)	13.9±2.1 (6-17)

Of the 130 ped-MS patients of the previous cohort we lost to follow-up 33 of them, mainly because they moved to other MS centers. Baseline characteristics are shown as number of cases (es. Female/Male) or as mean±standard deviation (range).

Treatments of the whole cohort

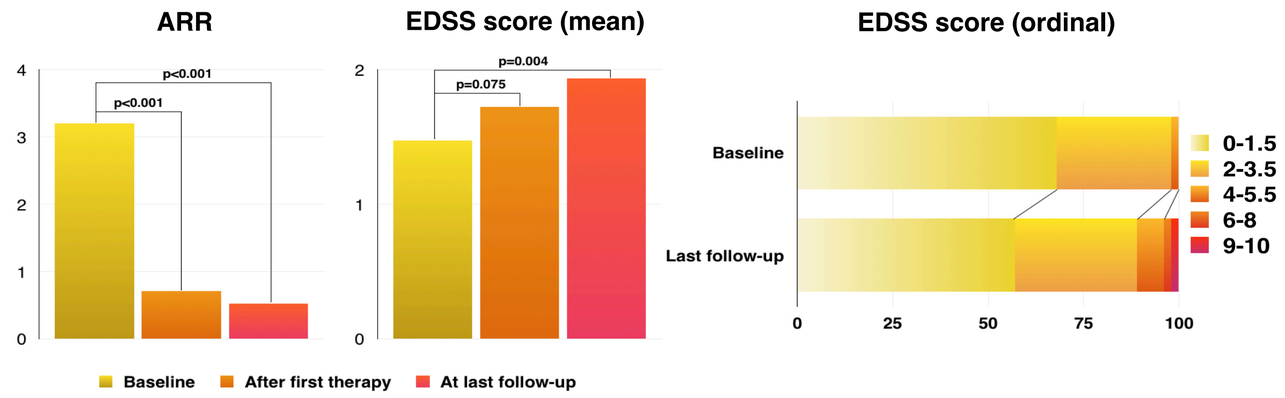


The figure shows baseline and subsequent therapies after a mean follow up of 12.5 years, according to three classification:

- Number of **switches** performed
- **Type** of therapy (Rx) received defined as first-line (IFN, GA, TFU, DMF) and second-line&others therapies (NAT, FTY, ALZ, SCT, CTX, MTX, AZA, IgV)
- **Last** ongoing therapy at the end of follow-up

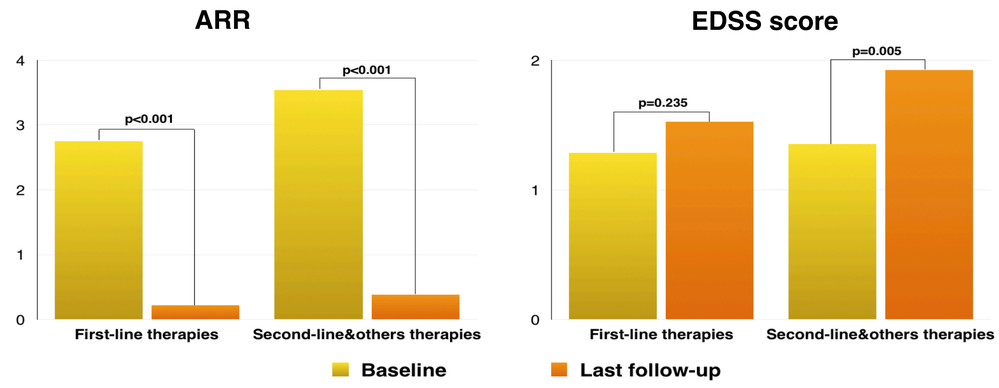
Legend: *Rx, therapy; IFN, interferon; GA, glatiramer acetate; TFU, teriflunomide; DMF, dimetilfumarate; NAT, natalizumab; FTY, fingolimod; ALZ, alemtuzumab; SCT, steam cell transplantation; CTX, cyclophosphamide; MTX, mitoxantrone; AZA, azathioprine; IgV, intravenous immunoglobulin; No tp, no therapy for at least 6 months).*

Clinical outcomes of the whole cohort



After the first therapy ARR drastically reduced with respect to the pre-therapy period, and it remained significantly low also at last observation. Mean EDSS score showed a slight increase after first therapy (not significant) and at last observation (significant). During the follow-up period one patient reached EDSS score of 10 and died because of MS, as shown in the bar graph on the right.

Clinical outcomes of the whole cohort according to type of therapy received



First-line and second-line&others therapies have been defined previously in the section "Treatments of the whole cohort". ARR was significantly reduced in both subgroups, while EDSS score showed a significant increase only in patients treated with second-line&other therapies.

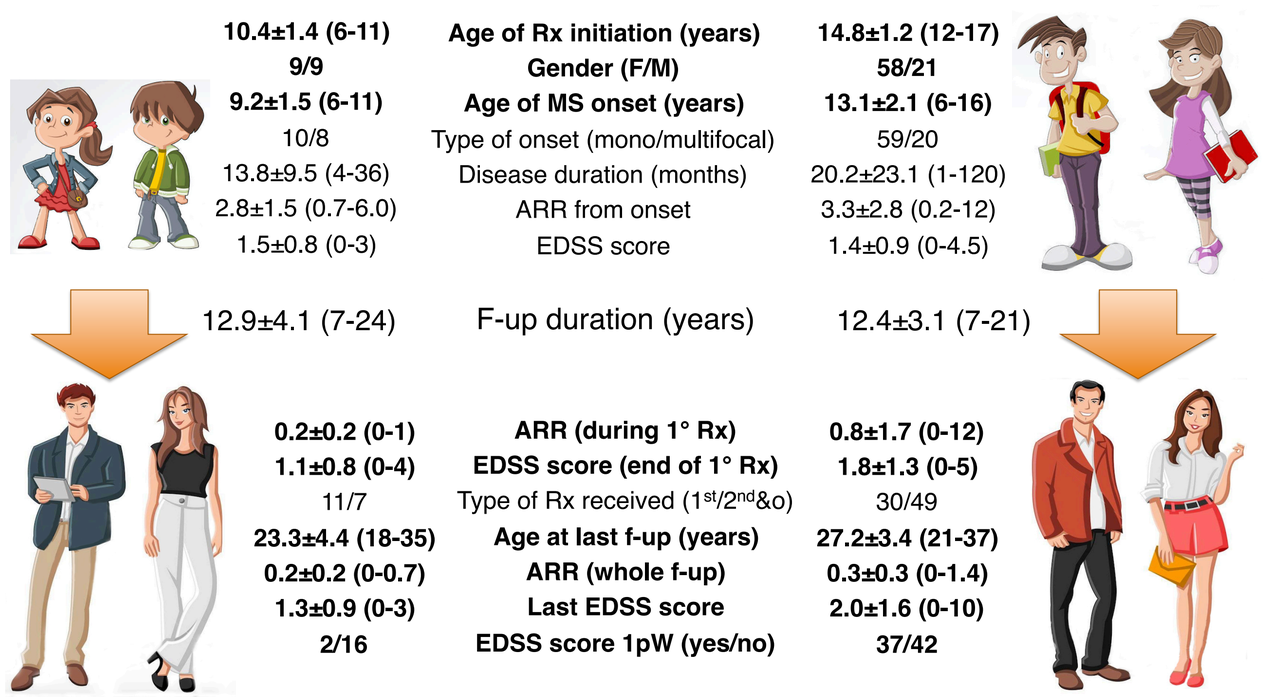
Baseline predictors of a worse MS course - multivariate analyses

Baseline variables	Last EDSS		ARR		EDSSw≥1p	
	B coefficient	p	B coefficient	p	Odds ratio	p
Age of onset (<12y/≥12y)	ns		ns		ns	
Age of therapy initiation (<12y/≥12y)	0.83 (0.17-1.49)	0.014	0.15 (0.01-0.28)	0.03	7.0 (1.5-32.7)	0.013
MS duration (months)	ns		ns		ns	
ARR	ns		ns		ns	
EDSS score	0.86 (0.57-1.15)	<0.001	ns		ns	
Clinical onset (mono/multifocal)	ns		ns		ns	
Gender (Male/Female)	ns		ns		ns	

Baseline EDSS score and starting therapy after 12 years (y) of age were predictors of the last EDSS score, while only starting therapy after 12y was a significant predictor of ARR during the whole follow-up and of EDSS score increment of ≥1 point at last observation (EDSSw≥1p).

Baseline characteristics and outcomes according to age of therapy initiation

<12 years old (18 pts)		≥12 years old (79 pts)
10.4±1.4 (6-11)	**Age of Rx initiation (years)**	**14.8±1.2 (12-17)**
9/9	**Gender (F/M)**	**58/21**
9.2±1.5 (6-11)	**Age of MS onset (years)**	**13.1±2.1 (6-16)**
10/8	Type of onset (mono/multifocal)	59/20
13.8±9.5 (4-36)	Disease duration (months)	20.2±23.1 (1-120)
2.8±1.5 (0.7-6.0)	ARR from onset	3.3±2.8 (0.2-12)
1.5±0.8 (0-3)	EDSS score	1.4±0.9 (0-4.5)
12.9±4.1 (7-24)	F-up duration (years)	12.4±3.1 (7-21)
0.2±0.2 (0-1)	**ARR (during 1° Rx)**	**0.8±1.7 (0-12)**
1.1±0.8 (0-4)	**EDSS score (end of 1° Rx)**	**1.8±1.3 (0-5)**
11/7	Type of Rx received (1st/2nd&o)	30/49
23.3±4.4 (18-35)	**Age at last f-up (years)**	**27.2±3.4 (21-37)**
0.2±0.2 (0-0.7)	**ARR (whole f-up)**	**0.3±0.3 (0-1.4)**
1.3±0.9 (0-3)	**Last EDSS score**	**2.0±1.6 (0-10)**
2/16	**EDSS score 1pW (yes/no)**	**37/42**



On the basis of multivariate analyses results we divided the whole cohort in two groups according to the age of therapy initiation (<12 and ≥12 years old). Baseline clinical characteristics and follow-up duration were similar, but clinical outcomes were better in the group starting therapy before 12 years of age. Bold variables have a statistically significant difference (p<0.05).

Legend: *pts, patients. Rx, therapy; f-up, follow-up; 1st, first line therapies as previously defined; 2nd&o, second-line and others therapies as previously defined; EDSS score 1pW, patients with a worsening of at least 1 point at last EDSS score.*

Conclusions

- Over 12 years of follow-up 43% of ped-MS patients remained on first-line therapies, while 57% patients switched to second-line or other treatments. At last observation about 15% of ped-MS patients was still on the first therapy;
- ARR was drastically reduced by the first treatment and remained low during the whole follow-up. This finding suggest that it is appropriate to shift soon non-responders to other treatment;
- At last observation the large majority of patients had an EDSS ≤ 3.5, about 10% had EDSS≥4, and one patients (≈1%) died because of MS;
- Starting therapy after 12 years of age was the main predictor of a worse MS course. This finding could be related to the higher inflammatory pattern of ped-MS, compare to the adult form, and to its better capability to compensate brain damage. This pattern could be even more relevant in the pre-pubertal stage;

References

1. Chitnis T, Tenembaum S, Banwell B, et al. Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis. Mult Scler. 2012;18:116-27.
2. Goodin, D.S., Frohman, E.M., Garmany, G.P. et al. Disease modifying therapies in multiple sclerosis: Subcommittee of the American Academy of Neurology and the MS Cuncil for Clinical Practice Guidelines. Neurology 2002, 58:169-178
3. Ghezzi, A., Banwell, B., Boyko, A. et al. The management of MS in children: A European view, Mult Scler. 2010, 16:1258-67
4. Ghezzi, A., Amato, M.P., Annovazzi, P. et al. Long-term results of immunomodulatory treatment in children and adolescents with multiple sclerosis: the Italian experience. Neurol. Sci. 2009, 30:193-199
5. Ghezzi A, Amato MP, Makhani N, et al. Pediatric multiple sclerosis: Conventional first-line treatment and general management. Neurology (suppl.) in press
6. E. Waubant, D. Chabas, MD, DT. Okuda et al. Difference in Disease Burden and Activity in Pediatric Patients on Brain Magnetic Resonance Imaging at Time of Multiple Sclerosis Onset vs Adults. Arch neurol/vol 66 (no. 8), Aug 2009
7. M.A. Rocca, M. Absinta, A. Ghezzi et al. Is a Preserved Functional Reserve a Mechanism Limiting Clinical Impairment in Pediatric MS Patients? Human Brain Mapping 30:2844–2851 (2009)
8. D. Chabas, MD, T. Castillo-Trivino, E.M. Mowry, et al. Vanishing MS T2-bright lesions before puberty. A distinct MRI phenotype? Neurology® 2008;71:1090–1093.