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Research article

Therapeutic options and outcomes in pediatric-onset multiple sclerosis with a focus on fingolimod—Eastern European tertiary center experience and literature review

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Abstract: Pediatric-onset multiple sclerosis (POMS) is a rare but increasingly recognized autoimmune condition affecting children under 18 years. The disease course is more aggressive than in adults, with frequent relapses, rapid accumulation of lesions, and early onset of motor and cognitive impairments. Due to limited approved disease-modifying therapies (DMTs) for children, first-line treatment often relies on injectable agents with moderate efficacy. Fingolimod, a high-efficacy therapy (HET), was recently approved for pediatric use, yet its uptake remains variable across regions. This retrospective, observational, monocentric study included 115 children diagnosed with POMS between 2018 and 2024 in a tertiary center in Romania. Patients were divided into three groups: 79 treated with interferon beta (IFNβ), 14 treated with fingolimod (FTY), and 22 untreated. We compared clinical outcomes, including annualized relapse rate (ARR), Expanded Disability Status Scale (EDSS) scores, and brain MRI lesion burden over 1 to 3 years of follow-up. Adverse events and treatment delays were also analyzed. All fingolimod-treated patients remained relapse-free during follow-up, while 42% of those on IFNβ experienced between 1 and 8 relapses. Fingolimod patients had significantly fewer new MRI lesions after 2 and 3 years of treatment ($p < 0.01$). EDSS scores remained stable or improved in both treated groups, with better outcomes in the FTY group. Adverse events included flu-like symptoms in all IFNβ-treated children and lymphopenia (mild to severe) in all FTY cases, managed by dose adjustment. Treatment initiation was delayed in the FTY group due to vaccination status and age-related barriers. Fingolimod demonstrated superior efficacy and comparable safety to IFNβ in pediatric MS. Our findings support early initiation of HETs in POMS and highlight real-world barriers to their implementation in Eastern Europe, including vaccination requirements and caregiver hesitancy.

Keywords: Pediatric multiple sclerosis; Fingolimod; Interferon beta; Disease-modifying therapies; High-efficacy treatment; MRI lesions; Relapse rate; EDSS

1. Introduction

Pediatric-onset multiple sclerosis (POMS) is a rare autoimmune demyelinating disorder, accounting for approximately 3–5% [1–4] of all multiple sclerosis (MS) cases. It is defined by clinical onset before the age of 18 years [5–7], and is characterized by a more inflammatory disease course compared to adult-onset MS. Children experience higher relapse rates, more extensive lesions visible on cerebral and spinal magnetic resonance imaging (MRI), and earlier onset of motor and cognitive impairments. Clinical relapses may present with a heterogeneous array of symptoms, including visual disturbances, balance and coordination deficits, motor and sensory impairments, sphincter dysfunctions, vertigo, and cognitive-behavioral changes [8–12]. Although disability accumulates more slowly than in adults [10,13–15], the earlier onset leads to a worse long-term prognosis [16–18]. Although POMS is rare, its incidence has increased over recent years due to improved diagnostic criteria and growing awareness [19–21]. Cognitive deficits may be present early in up to 30% of pediatric cases, significantly impacting quality of life [22–24]

Despite improved diagnostic criteria and growing interest in pediatric MS, treatment remains a significant challenge due to the limited number of approved disease-modifying therapies (DMTs) for children [25–28]. In Romania, POMS treatment is provided through the National Program for Rare Diseases, using internationally approved molecules. Interferon beta (IFNβ) has been available since 2010, while fingolimod (FTY) was included in 2022. Dimethyl fumarate and teriflunomide have also been recently approved and are expected to be implemented soon. According to current national regulations, newer therapies can only be administered within clinical trials or off-label, pending FDA, EMA, and national approval.

Most first-line treatments continue to rely on injectable DMTs such as IFNβ, with moderate efficacy and limited long-term adherence in pediatric populations [29–32]. Studies show comparable long-term outcomes between children and adults treated with IFNβ [27,33–39], but newer molecules such as dimethyl fumarate [39] and high-efficacy therapies (HETs) including fingolimod, natalizumab, and ocrelizumab have demonstrated greater efficacy [35,40–43].

Fingolimod, an oral sphingosine-1-phosphate receptor modulator, was the first high-efficacy therapy (HET) approved for pediatric use after the pivotal PARADIGMS trial demonstrated its superiority over IFNβ-1a in reducing relapse rates and new MRI lesions [42,43]. It acts by sequestering lymphocytes in lymph nodes, thereby reducing central nervous system (CNS) inflammation [35,44,45], with a safety profile comparable to that in adults [45,46]. However, access to fingolimod and other HETs remains inconsistent across Eastern Europe due to systemic barriers such as cost, regulatory delays, incomplete vaccination schedules, and caregiver hesitancy [18,25,47–49]. Until recently, many cases required off-label treatment with natalizumab, ocrelizumab, or rituximab [50–54], often guided by local availability and clinical urgency.

Moreover, data on real-world treatment outcomes in this region remain scarce. Existing studies—such as those by Brola and Bizjak (Poland and Slovenia) [55,56], Afanasjeva and Krajnc (Lithuania and Slovenia) [57,58], Menascu (Israel and Czech Republic) [59], and Bykova, Steczkowska, and Popova (Russia) [60–62] —have addressed various aspects of POMS, including demographics, clinical features, and treatment results, but Romania lacks published data on this topic.

The aim of this study was to evaluate the efficacy and safety of fingolimod compared to interferon beta in a real-world cohort of children with POMS from a Romanian tertiary center. We also aimed to assess clinical outcomes in terms of relapse rate, disability progression, and MRI lesion burden. We hypothesized that fingolimod would provide superior disease control compared to IFNβ, despite regional challenges to early HET access.

2. Materials and Methods

Study Design and Participants

This retrospective, observational, longitudinal study was conducted at the Pediatric Neurology Department of Prof. Dr. Alexandru Obregia's Clinical Hospital, Bucharest, Romania. A total of 115 children under the age of 18 years were diagnosed with pediatric-onset multiple sclerosis (POMS) between January 2018 and December 2024. Based on treatment status, the patients were divided into three groups: 22 untreated, 79 treated with interferon beta (IFNβ), and 14 treated with fingolimod (FTY).

From the initial cohort of 120 children, five were excluded due to insufficient sample size for treatment subgroup analysis: three received rituximab, one dimethyl fumarate, and one corticosteroids only.

Treatment Allocation and Criteria

The 14 patients in the fingolimod group received FTY as first-line therapy either due to age (it was the only available option for patients aged 10–12 years), or due to very active forms of POMS. These were defined as: ≥2 clinically confirmed relapses within one year, accumulation of new lesions on T2-weighted sequences or contrast-enhancing lesions on brain MRI compared to previous scans. One patient received FTY off-label before age 10. FTY was also used as second-line therapy in cases where IFNβ proved inefficient.

Clinical and MRI Evaluation Protocol

MRI assessment included both brain and spinal cord imaging at baseline, with contrast enhancement. Cerebral MRIs were repeated at 6 months, annually, and during relapses or treatment switch. Spinal MRIs were performed at baseline and subsequently at 1–2 year intervals or when symptoms suggested spinal involvement. Before patients turned 18, full CNS imaging was repeated.

Imaging was performed using 1.5 Tesla MRI scanners. Protocols followed the recommendations of the International Society for Multiple Sclerosis [63,64], except for the omission of the 3D T1 sequence. Slice thickness ranged from 1 to 3 mm (occasionally 4 mm, depending on equipment). Sedation was required for two patients under the age of 7. Comparative analysis of serial MRIs was used to detect new lesions or the extension of existing ones.

All MRIs were interpreted by neuroradiologists specialized in autoimmune demyelinating disorders, with particular attention to differential diagnosis from neuromyelitis optica spectrum disorder (NMOSD) and MOG antibody disease (MOGAD) [65,66].

Treatment Regimens

IFNβ was administered in three formulations:

- IFNβ-1a intramuscular (Avonex) – 30 mcg once weekly
- IFNβ-1a subcutaneous (Rebif) – 44 mcg three times weekly
- IFNβ-1b subcutaneous (Betaferon) – 250 mcg every other day

Fingolimod (Gilenya) was administered orally once daily in doses adjusted for weight:

- 0.5 mg/day for patients >40 kg
- 0.25 mg/day for patients <40 kg

Outcomes and Statistical Analysis

Primary endpoints included relapse frequency, EDSS progression, and the number of new MRI lesions. Data were collected from medical records. SPSS version 22 was used for statistical analysis. Descriptive statistics were applied, and the Kruskal-Wallis and Chi-square tests were used to compare groups. For group homogeneity, 15 IFNβ patients were randomly selected for direct comparison with the FTY group.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee of Prof. Dr. Alexandru Obregia's Clinical Hospital (approval number 8377/25.03.2025). Written informed consent was obtained from the parents or legal guardians of all participants.

3. Results

From the initial cohort of 120 patients diagnosed with pediatric-onset multiple sclerosis (POMS), five were excluded due to alternative or incomplete treatment (three received rituximab, one dimethyl fumarate, and one oral corticosteroid only).

A total of 115 patients were included in the final analysis and divided into three groups: 79 treated with interferon beta (IFNβ), 14 with fingolimod (FTY), and 22 untreated. Figure 1 presents the patient selection and allocation process.

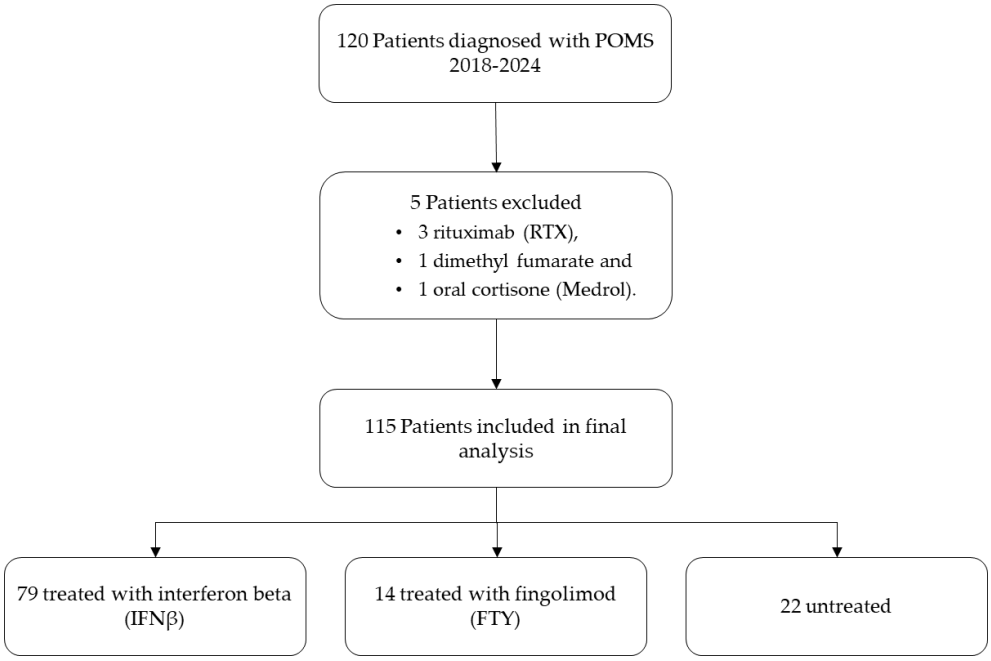

Figure 1. Flowchart of patient selection, exclusion and treatment group allocation in the study

The study cohort included 115 participants, with a female-to-male ratio of 2:1 (77 girls and 38 boys). Patients were divided into three groups: 79 received interferon beta (IFNβ), 14 were treated with fingolimod (FTY), and 22 received no disease-modifying treatment.

Within the IFNβ group, 44 patients received intramuscular IFNβ-1a (Avonex), 27 received subcutaneous IFNβ-1a (Rebif), and 8 were treated with subcutaneous IFNβ-1b (Betaferon). These subgroups were analyzed collectively as the "IFNβ group."

Most untreated patients (n = 20) and the majority of those in the IFNβ group (n = 73) had late-onset MS (diagnosed after age 12). In the fingolimod group, 4 patients had early-onset MS (under age 10), 5 had disease onset between 10 and 12 years, and 5 were diagnosed after age 12. The demographic and baseline clinical characteristics are summarized in Table 1.

Among the 79 children treated with IFNβ, 62 initiated treatment within 6 months of diagnosis, and 33 of them started within the first 3 months. In the fingolimod group, 11 patients began therapy within the first year after diagnosis (7 of them within the first 6 months), while the remaining 3 initiated fingolimod between 1 and 2 years post-diagnosis (Table 1).

Reasons for delayed or absent treatment in the untreated group included: patients nearing the age of 18 with anticipated adult care and access to high-efficacy therapies (n = 7), parental decision to postpone treatment (n = 9), incomplete diagnostic work-up or failure to meet McDonald criteria (n = 3), and the presence of severe depression at a time when only IFNβ was available (n = 3).

In the IFNβ group, treatment initiation was delayed in 16 cases due to caregiver reluctance toward injectable therapies and in 8 cases due to delayed referral to a pedi-

atric neurologist. Among fingolimod-treated patients, treatment initiation was postponed in 9 cases due to incomplete vaccination records, and in 3 cases due to young age at diagnosis (Table 1).

Table 1. Demographic and clinical characteristics of patients

Item	Group 1 (without treatment) N=22	Group 2 (IFNβ) N=79	Group 3 (Fingolimod) N=14
Gender (female:male)	2:1	2:1	1:1
Age of onset			
<10 years	2	3	4
10-12 years	0	3	5
>12 years	20	73	5
Age of MS diagnosis			
<10 years	1	0	3
10-12 years	1	2	3
>12 years	20	77	8
Duration diagnosis-treatment (months)			
<6 mo	NA	62	7
> 6 mo	NA	17	7
Reasons for delaying treatment initiation/NO treatment			
short time until they turned 18	7	3	0
Not meet McDonald crit/ incomplete investigations	3	3	9 (vaccination)
the family wants to delay therapy	9	16	2
late presentation to the doctor	0	8	0
depression	3	0	0
young age (<10years)	0	0	3
Relapse no before dg	1ep-15p; 2ep-6p; 3ep-1p	1ep-46p; 2ep- 23p; 3/4ep-9/1p	1ep-8p; 2ep-6p
Relapse no between dg-tratment starts	NA	0ep-62p; 1ep-11p; 2/3ep-5/1p	0ep-6p; 1ep-5p; 2/3/4ep-1/1/1p
Relapse no with treatment	NA	0ep-46p; 1ep-19p; 2/3ep-7/5p; 4/8ep-1/1p	0
Total no of relapses	1ep-11p; 2ep-8p; 3ep-3p	1ep-26p; 2ep-20p; 3/4ep-	1/2/3ep-3p each; 4/7/8ep-

		14/12p; 5/6ep-3p each; 8ep-1p	1p each; 6ep-1p
Duration 1st -2nd relapse (months)			
1-12 mo	8	36	6
12-36 mo	3	12	2
>36 mo	0	4	3
Duration 2nd – 3th relapse (months)			
6-12 mo	2	17	4
12-36 mo	2	16	4
>36 mo	0	0	0
duration between attacks under treatment			
1-12 mo	NA	10	0
12-36 mo	NA	0	0
duration of treatment			
~12 mo	NA	31	6
12-36 mo	NA	40	6
>36 mo	NA	8	2
Type and severity of adverse reaction (AR)			
lymphopenia >0.6 (mild AR)	NA	NA	6
lymphopenia 0.4-0.6 (mild AR)	NA	NA	5
lymphopenia 0.2-0.39 (moderate AR)	NA	NA	3
flu-like symptoms (mild AR)	NA	79	NA
local inflammation (moderate AR)	NA	1	NA
Initial chronic treatment	NA	84	9
Actual chronic treatment	NA	79	14
No of chronic treatments	NA	1tt-77p; 2tt-2p	1tt-8p; 2tt-4p; 3tt-1p; 4tt-1p
EDSS 1-3y after dg			
1-2	year 1-2p year 2-2p year 3-2p	year 1-15p year 2-13p year 3-11p	year 1-2p year 2-3p year 3-2p
2.5-3	year 3-1p	year 1-2p year 2-2p year 2-2p	year 3-1p
>3	0	year 3-1p	0
EDSS at 1-3y of trat			
1-2	NA	year 1-11p year 2-8p year 3-8p	year 1-3p year 2-1p year 3-1p

2.5-3	NA	year 1-3p year 2-2p year 3-1p	year 1-1p
>3	NA	0	0
Actual/Last EDSS			
1-2	1	15	3
2.5-3	1	3	1
>3	0	0	0
Brain MRI 6mo-3y after dg, no of new lesions			
>10	0	year 1-1p	year 1-1p
6-10	year 1-12p,	year 1-59p,	year 1-10p,
1-5	year 2-8p, Year 3-3p	year 2-42p, year 3-24p	year 2-7p, year 3-4p
Brain MRI 6mo-3y of treat, no of new lesions			
6-10	NA	year 1-48p year 2-27p	0
3-5	NA	year 3-9p	year 1-9p year 2-3p
1-2	NA	year 3-15p	year 3-3p

Legend: ep=episode; p=patient (eg. 1ep-26p-->26 patients had only one episode (relapse)); tt=treatment.

Relapse distribution before and after treatment initiation

Prior to starting therapy, most IFNβ-treated patients (n = 46) had experienced a single relapse, while 23 had two relapses and 10 had three to four relapses. In the fingolimod group, 8 patients had one relapse and 6 patients had two relapses prior to treatment initiation, consistent with highly active disease forms. Among untreated patients, 15 experienced a single relapse, 6 had two relapses, and 1 patient had three relapses before treatment could be initiated.

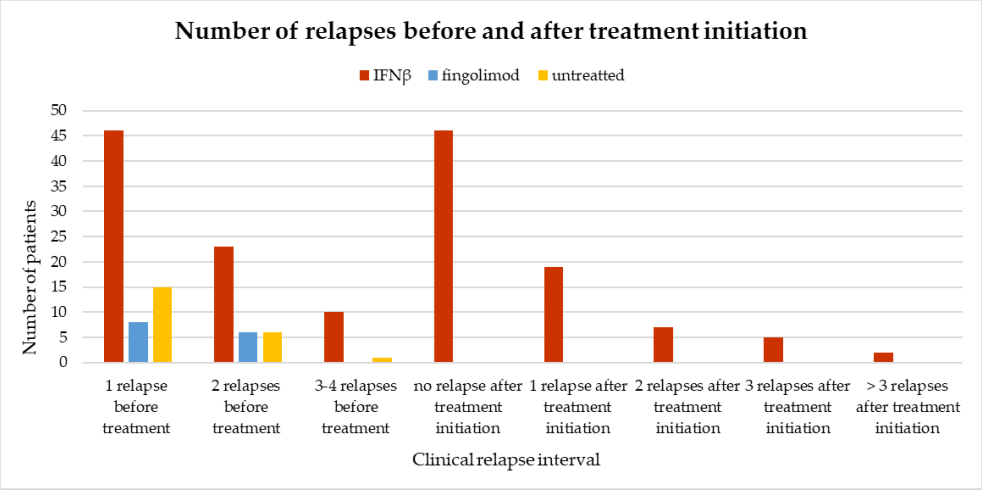

Figure 2. Distribution of relapses before and after treatment initiation across the three groups

Table 2. Kruskal Wallis and Chi-squared Tests

	X^2	df	p
no relapses before diagnosis	6.55	12	0.248
no of relapses from diagnosis to treatment	17.46	20	0.391
no of relapses with treatment	25.02	20	0.011
duration between attacks1_attack2	22.75	16	0.535
duration between attacks2_attack3	19.57	16	0.250
duration of monitorization	53.34	16	< .001
mild adverse reactions	235.10	16	< .001
moderate and sever adverse reactions	174.52	20	< .001
Current EDSS _ final monitoring period when turning 18 years old	31.46	12	0.0002
EDSS 6 months after dg	19.52	16	0.232
EDSS 1 year after dg	7.12	16	0.712
EDSS 2 years after dg	15.11	16	0.560
EDSS 3 years after dg	14.11	16	0.490
EDSS at 1st year of treatment	113.99	16	< .001
EDSS at 2nd year of treatment	38.90	16	< .001
EDSS at 3rd year of treatment	31.79	16	< .001
no new brain lesions - MRI at 6 mo after dg	10.41	16	0.444
no new brain lesions - MRI at 1y after dg	19.07	20	0.517
no new brain lesions - MRI at 2y after dg	12.31	20	0.182
no new brain lesions - MRI at 3y after dg	10.71	20	0.552
no new brain lesions - MRI at 1st year of treatment	32.40	16	0.0009
no new brain lesions - MRI at 2nd year of treatment	56.56	16	< .001
no new brain lesions - MRI at 3rd year of treatment	18.58	12	< .001

From diagnosis to treatment initiation, 62 IFNβ-treated patients had no relapses, while 11 experienced one relapse. In the fingolimod group, 6 had no relapses and 5 had one inflammatory event during this period. Differences between groups were not statistically significant ($p > 0.05$; Tables 1 and 2).

Under treatment, 46 patients in the IFNβ group and all 14 in the fingolimod group remained relapse-free. However, 33 patients in the IFNβ group experienced between 1 and 8 relapses during treatment. This difference between groups was statistically significant ($p < 0.05$; Tables 1 and 2).

The interval between the first and second relapse was 1–12 months in 8 untreated, 36 IFNβ-treated, and 6 fingolimod-treated patients. Between the second and third relapse, only 2 untreated, 17 IFNβ-treated, and 4 fingolimod-treated participants had a 6–12 month interval. Ten IFNβ-treated patients had relapses during the first year of immunomodulatory therapy. However, no statistically significant differences were observed in relapse timing across the three groups ($p > 0.05$; Tables 1 and 2).

Treatment duration varied: 50.6% (n=40) of the IFNβ group and 42.8% (n=6) of the fingolimod group received therapy for 1–3 years, while 10.1% (n=8) and 14.2% (n=2), respectively, were treated for over 3 years. Differences in monitoring time were statistically significant ($p < 0.01$; Tables 1 and 2).

Regarding safety, lymphopenia was noted in all fingolimod patients: 6 mild, 5 moderate, and 3 severe cases. Those with severe lymphopenia received alternate-day

dosing, leading to improved lymphocyte counts and good outcomes. One child, due to low weight (<40 kg), received 0.25 mg/day; the rest received 0.5 mg/day (Table 1).

All IFNβ-treated children experienced mild flu-like symptoms (headache, shiver, fever, myalgia, fatigue) in the first 24 hours after administraton, especially in the first 2–3 months. One child developed severe local inflammation due to improper administration; treatment was paused for one month, then resumed without further complications (Table 1).

Initially, 84 patients received IFNβ; 2 switched between IFNβ subtypes, and 5 switched to fingolimod. Of these 5, two had received intravenous immunoglobulins and one had been co-treated with azathioprine due to high disease activity and lack of alternatives. Nine patients received fingolimod as first-line treatment; 2 additional cases received it briefly between IFNβ and rituximab due to liver side effects or disease progression. These 2 were excluded from analysis.

Regarding the number of brain lesions before treatment, 12 children from the untreated group had between 6 and 10 brain lesions in the first year after disease onset, 8 and 4 patients, respectively had 1 to 5 new lesions in the second and third year after condition started. In the first 3 years of disease onset, 59, 42 and 24, respectively from the interferon subjects had between 6 and 10, then 1 and 5 new brain lesions. In contrast, 10 of the Fingolimod patients had between 6 and 10 brain lesions in the first year after disease started, 7 of them had 1 to 5 new lesions in the second year and 4 had 1 to 5 inflammatory lesions in the third year from onset. There were no statistically significant differences between the untreated group, the interferon group, and the Fingolimod group regarding brain lesions in the first 3 years after diagnosis, $p>0.05$ (Table 1 and 2).

In the first 2 years after starting interferon beta treatment, most patients--48 and 27, respectively, had 6-10 brain lesions and, in the third year after starting treatment, only 9 patients had between 3 and 5 new lesions. However, 9 then 3 children with Fingolimod had 3 to 5 new brain lesions in the first 2 years with treatment and, in the third year after starting treatment 3 subjects had 1 to 2 new lesions. There were statistically significant differences between the untreated group, the interferon group and, the Fingolimod group as number of new cerebral lesions in the first 3 years of treatment, $p<0.01$ (Table 1 and 2). MRI follow-up emphasized the presence or absence of new T2 or contrast-enhancing lesions. In this study, we focused primarily on the number of new lesions rather than their exact location or volumetric size.

The EDSS score in the first 2 years after diagnosis showed mild impairment for 2 untreated patients each year. In the third year after diagnosis, the EDSS score for 2 untreated subjects revealed mild impairment and for 1 child moderate problems. For most interferon participants, the EDSS scores in the first year after diagnosis showed mild impairment (n=15), then in the second year after diagnosis 13 children had mild and 2 had moderate deficits and, in the third year after diagnosis mild modifications were seen in 11 subjects, moderate in 2 and severe in 1 patient. For Fingolimod patients, the EDSS score in the first 2 years after diagnosis revealed mild impairment in 2 kids and one, respectively, then in the third year after diagnosis 2 participants had mild and one moderate deficits. There are no statistically significant differences between the no treatment group, the interferon group and the Fingolimod group in terms of EDSS scores in the first 3 years after diagnosis, $p>0.05$ (Table 1 and 2, Figure 3 and 4).

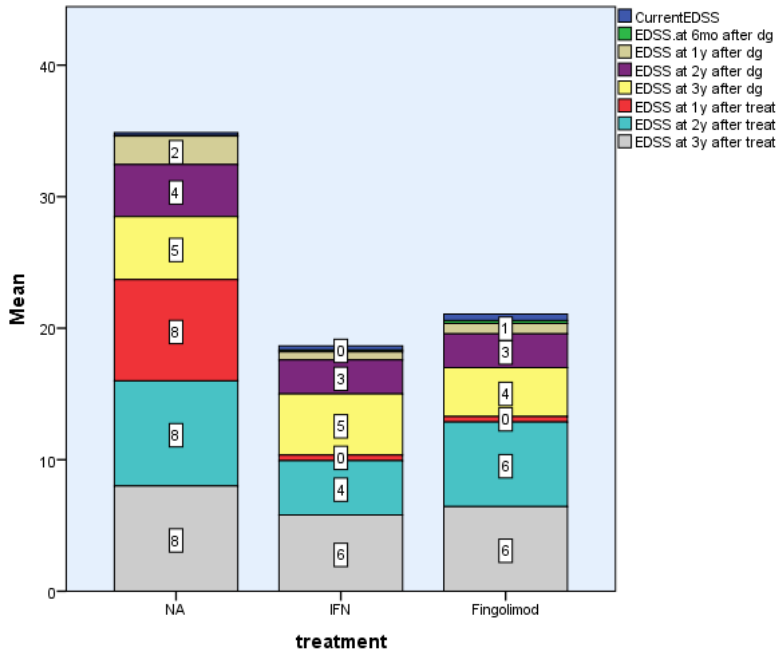

Figure 3. EDSS score

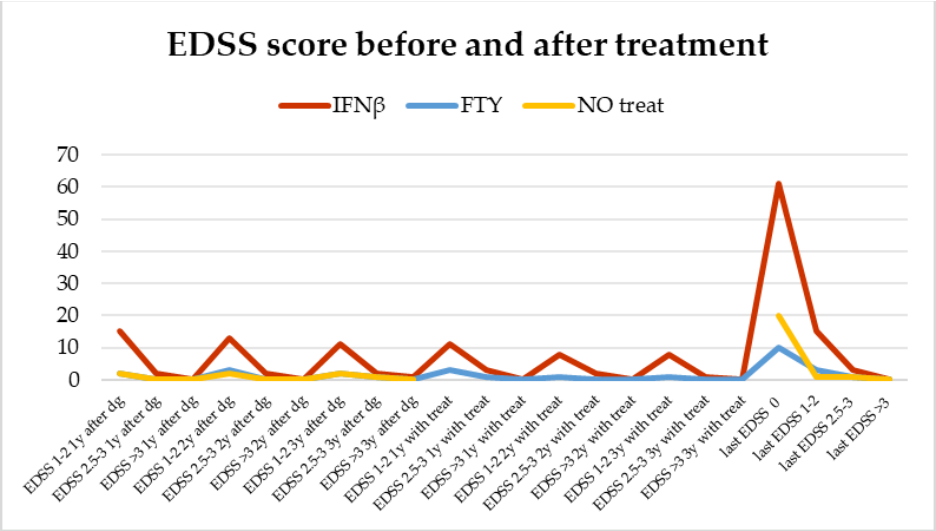

Figure 4. EDSS score distribution by treatment group, before and after treatment initiation

After initiation of treatments, the following changes occurred: in the first year of treatment 11 patients with IFNβ had mild impairment and 3 participants had moderate; while 3 subjects treated with FTY had mild deficits, in the first year of treatment. Only one child on Fingolimod after the first year of treatment had moderate impairment. In the second year of treatment the changes in the level on the EDSS scale were: 8 participants with IFNβ had mild and 2 had moderate deficits and one patient with Fingolimod had mild EDSS modification. After 3 years of treatment 8 children treated with interferon had mild impairment and one moderate problems, while one patient with Fingolimod had mild deficits. Currently, in all groups the EDSS is mildly modified for one untreated patient, 15 IFNβ subjects and, 3 FTY participants. There are statistically significant differences between the untreated group, the interferon group and, the fingolimod group in terms of EDSS scores between 6 months and 3 years after treatment initiation, $p<0.01$ (Table 1 and 2, Figure 5).

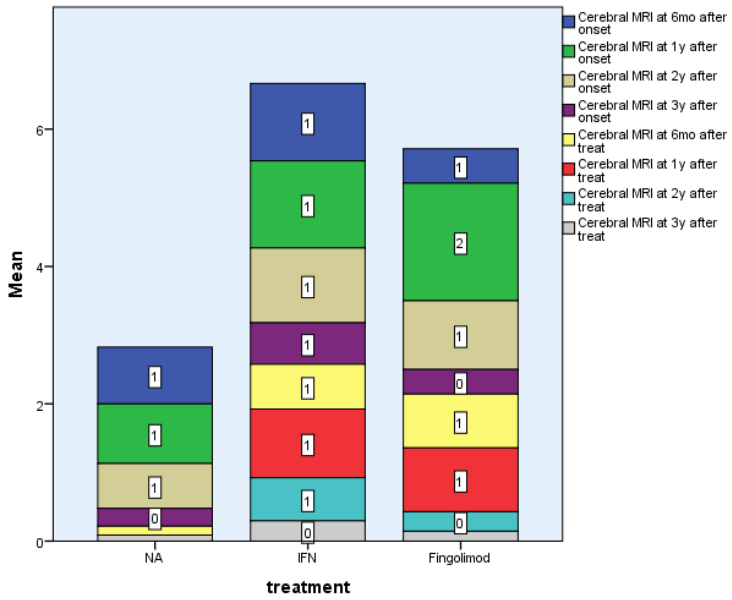

Figure 5. Cerebral MRI after diagnosis and treatment starts

Except for those mentioned above the rest of the subjects had EDSS score 0 at the last evaluation with no obvious motor deficits.

4. Discussion

This retrospective, longitudinal study conducted over a 7-year period (2018–2024) evaluated the safety and efficacy of chronic treatment with interferon beta (IFNβ) and fingolimod (FTY) in pediatric-onset multiple sclerosis (POMS). A total of 115 patients were included: 79 treated with IFNβ, 14 with FTY, and 22 untreated. The study aimed to compare clinical and imaging outcomes between these groups and to highlight the importance of initiating high-efficacy therapies (HET) as first-line treatment in POMS. As there are few studies from Eastern Europe and none from Romania, our findings contribute valuable regional data, considering the local challenges that often delay treatment, including incomplete vaccination and limited access to newly approved molecules.

This study also revealed a female-to-male ratio of 2:1 (77:38), consistent with existing literature, though the FTY group had a balanced gender distribution (7:7), likely due to the younger age of these patients. Female predominance in MS typically becomes apparent after puberty [41–43,54].

Our results indicate that fingolimod provided superior disease control compared to IFNβ, both clinically and radiologically. These findings are consistent with previously published data [67], including the PARADIGMS trial and real-world studies by Chitnis et al. [42], Spelman et al. [41], and Deiva et al [54]. In our cohort, all patients in the FTY group remained relapse-free, while 33 (42%) in the IFNβ group experienced relapses. The untreated group maintained a similar annual relapse rate throughout. These findings support the superiority of treated over untreated cases, even when the therapy used is of only moderate efficacy. Chitnis et al. reported relapse rates of 0.12 for fingolimod versus 0.67 for IFNβ-1a, an absolute difference of 0.55 relapses (relative difference: 82%, $p < 0.001$) [42]. Spelman et al. confirmed the efficacy of fingolimod in significantly reducing relapse risk (HR = 0.49) [41]. Deiva et al. reported reductions in ARR and T2 lesions by 85.8% and 53.4%, respectively, versus IFNβ, with even higher rates for younger patients (≤12 years): 91.9%-94.6% [54].

MRI monitoring further confirmed the treatment effects. While pre-treatment lesion counts were comparable, post-treatment comparisons showed substantial reduction in new cerebral lesions in both groups, more prominently in the FTY group. In the IFNβ group, 48 (60%) patients had 6–10 new lesions in the first year, 27 (34%) in the

second, and 24 (30%) in the third. In contrast, 9 (64%) of the FTY group had fewer than five lesions in year one, increasing to 11 (80%) by year two, with similar rates maintained in year three. Arnold et al. [43], reported similar findings, with fingolimod reducing new/increasing T2 lesions by 52.6%, new T1 Gd+ lesions by 66.0%, new T1 hypointense lesions by 62.8%, and combined unique active (CUA) lesions by 60.7%, all with $p < 0.001$.

No significant differences in EDSS scores were noted between groups prior to treatment. Following treatment initiation, however, 11 (14%) IFNβ patients showed mild and 3 (4%) moderate impairment after one year. Over the next two years, 8 (10%) had mild and 2 (2%) moderate impairments. In the FTY group, 3 (20%) had mild and 1 (7%) moderate impairment after one year, with only 1 (7%) showing mild deficits thereafter. These results reflect an approximate 30% improvement in the IFNβ group and 70% in the FTY group by the end of the first year. Piri Cinar [68] also reported low EDSS levels in pediatric patients treated with fingolimod. In their study, baseline EDSS scores were 1.5 in the FTY group and 1.6 in the IFNβ-1a group, with a 77.2% lower risk of EDSS progression in the FTY group. Deiva et al. found modified EDSS scores at study end in 20.6% vs. 10.5% ($p = 0.043$) for IFNβ vs. FTY [54]. These findings are consistent with other studies and case reports [33,35,69,70].

Adverse events were mild and manageable. IFNβ-related side effects included flu-like symptoms (headache, fever, fatigue), particularly in the initial months. All FTY-treated patients developed lymphopenia, including three with severe forms that required dose adjustments. No patient discontinued treatment due to adverse effects. These findings are in line with published data and reinforce the favorable safety profiles of both therapies [48,50,54,68,71].

This study also underscores region-specific barriers to early HET access. Treatment delays were longer in the FTY group, largely due to pre-treatment requirements such as vaccination status and parental hesitation. These challenges are frequently underreported in clinical trials but represent significant hurdles in real-world clinical practice.

In conclusion, our findings support the early use of fingolimod in pediatric MS, even as a first-line therapy in highly active disease. The data reinforce its superior efficacy, tolerability, and safety when compared to IFNβ. We also emphasize the importance of continued comparative studies, particularly with emerging CD20 monoclonal antibodies, to optimize therapeutic strategies in POMS.

Limitations and Future Research Directions

This study has several limitations. First, the number of patients treated with fingolimod was relatively small, and the treatment duration was limited to approximately two years, which may affect the generalizability of the long-term outcomes. Second, the retrospective design inherently introduces selection bias and limits control over confounding variables. Third, although MRI follow-up was systematically performed, slight variability in protocols (e.g., image thickness, absence of 3D T1 sequences) across centers may have influenced lesion detection accuracy. We also focused on lesion count rather than volumetric analysis or lesion localization.

In addition, real-world treatment delays related to systemic barriers—such as incomplete vaccination status and caregiver hesitation—may have influenced treatment timing and outcomes in the FTY group. These contextual factors, specific to the local healthcare setting, warrant further investigation.

Future studies should aim for prospective, multicenter designs involving larger POMS cohorts and direct comparison between HET options, including newer anti-CD20 monoclonal antibodies. Investigating cognitive outcomes, long-term disability trajectories, and patient-reported outcomes would further enhance our understanding of pediatric MS management.

4. Conclusions

This study provides the first real-world comparative data on pediatric MS treatment outcomes from Romania, highlighting the clinical and imaging benefits of fingolimod over interferon beta in a real-life Eastern European setting. Despite treatment delays and logistical barriers, fingolimod showed superior efficacy in preventing relapses, reducing lesion burden, and maintaining functional status. The safety and tolerability profile remained favorable throughout follow-up. Our findings underscore the urgent need for timely access to high-efficacy therapies in POMS and the removal of systemic obstacles such as vaccination prerequisites and parental uncertainty. Implementation of early, targeted treatment strategies is essential to prevent long-term disability. Ongoing clinical trials and regional collaboration are needed to refine therapeutic approaches and ensure equitable care for children with MS.

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Abbreviations

The following abbreviations are used in this manuscript:

HET	High efficacy therapy
DMT	Disease modifying therapy
EOS	End of study
MRI	Magnetic Resonance Imaging
POMS	Pediatric onset Multiple Sclerosis
IFNβ	Interferon beta
FTY	Fingolimod
CUA	Combined unique active
EDSS	Expanded disability status scale

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