

Pediatric multiple sclerosis

Conventional first-line treatment and general management

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ABSTRACT

Many disease-modifying therapies are currently available for adults with relapsing-remitting multiple sclerosis (MS) but none of them has been tested in pediatric MS in randomized placebo-controlled trials. At present, as suggested by observational studies and experts' guidelines, interferon- β and glatiramer acetate continue to be the standard first-line treatments for pediatric MS. Observational studies and some controlled unblinded trials have shown a positive effect of these medications in reducing relapse rate and delaying disease progression, with an acceptable safety profile. The goal of this article is to provide an overview of current knowledge with regard to safety, tolerability, and efficacy of first-line treatment options for MS in the pediatric age group, with the aim of providing guidance for planning first-line treatment of MS in children and adolescents. *Neurology*® 2016;87 (Suppl 2):S97-S102

GLOSSARY

DMT = disease-modifying therapies; **GA** = glatiramer acetate; **IFN- β** = interferon- β ; **MS** = multiple sclerosis; **NAb** = neutralizing antibodies; **RRMS** = relapsing-remitting multiple sclerosis.

Many disease-modifying therapies (DMT) are currently available for adults with relapsing-remitting multiple sclerosis (RRMS), including interferon- β (IFN- β) 1a/1b, glatiramer acetate (GA), teriflunomide, dimethyl fumarate, natalizumab, fingolimod, and alemtuzumab. Their effectiveness has been demonstrated by phase 3 studies and by observational postmarketing studies for some.¹⁻⁵ IFN- β , GA, and teriflunomide have also been tested in patients with clinically isolated syndrome (CIS), and have been found to reduce the risk of a subsequent attack.⁶⁻¹⁰ Results are disappointing in the treatment of secondary progressive multiple sclerosis (MS) as only IFN- β was shown to reduce the progression if administered to patients with a residual inflammatory component.^{11,12}

No medication currently approved for adults with RRMS has completed testing for pediatric MS in randomized placebo-controlled trials, although several pediatric MS trials have recently been launched. Use of DMT in pediatric MS remains off-label in many countries, especially in patients younger than 12 years; nevertheless, these medications are widely used.

The high frequency of relapses in pediatric 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.^{1,3}

Recent volumetric MRI data have demonstrated that pediatric patients with MS have a smaller overall brain volume than would be expected for age,¹³ in spite of the purported higher capability to compensate for brain damage,¹⁴ suggesting that demyelinating lesions can also affect overall brain growth and development. It is also important to note that cognitive dysfunction occurs in about 1/3 of children and adolescents with MS. These findings additionally support the view that pediatric MS is not a benign disorder, again reinforcing the need to treat these patients early.

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In comparison to adult MS patients, time between MS onset and accumulation of disability is longer in patients with pediatric MS, suggesting that children with MS have a higher capability to compensate for inflammatory brain damage despite high relapse rates. Conversely, the time to progress from mild to severe disability (about 10 years) is similar in children and adults,¹⁵ suggesting that this interval is relatively fixed, not age-dependent, and mainly driven by neurodegeneration. However, given their younger age at onset, pediatric patients with MS reach both mild and severe disability at a younger age. Taken together, these data indicate that it is appropriate to intervene early to prevent disease progression. The adult-onset MS experience suggests that DMTs are more effective if administered early in relapsing MS.^{4,5}

CURRENT VIEWS OF FIRST-LINE TREATMENT IN PEDIATRIC MS The efficacy and safety of IFN- β and GA in pediatric MS has been assessed by several phase 4 observational studies whereas comparable information is not currently available on the use of teriflunomide, dimethyl fumarate, and fingolimod. Pediatric trials with these agents are ongoing and their use in children with MS should generally occur in the context of controlled clinical trials, or considered with extreme caution in selected cases, until data on their effectiveness, tolerability, and safety are available.

Two position papers^{1,3} have reported data on the use of IFN- β and GA in pediatric patients: results are summarized in table 1.^{15–25} Data from observational studies are available in about 600 patients treated with IFN- β : 7 studies included >20 patients; 6 have a follow-up of 2 years or more.

Two studies have compared pediatric patients with MS treated with IFN- β with a control group.^{24,26} In one unblinded study, 16 patients were randomized to intramuscular IFN- β -1a, half of adult dose, once a week or to no treatment. After 4 years, relapse rates ($p = 0.04$), disability progression ($p = 0.01$), and new T2 lesions ($p = 0.006$) were lower in treated vs untreated patients.²⁶ In another study, controls were extracted from a database: after a mean follow-up of 5.5 years, patients treated with IFN- β demonstrated significantly reduced occurrence of relapses, especially in the first 2 years of exposure, and a decrease in development of severe disability, although not statistically significant²⁴ (table 1).

Most studies have demonstrated a favorable effect of IFN- β on pediatric MS evolution, with a decline of relapse rate during the treatment phase, compared to

the pretreatment period. The level of disability remained unchanged at the last observation in the majority of studies. There are no data suggesting that one drug is better than another, so the final choice is made by the treating physician after consideration of side effects, route, and frequency of administration with the patient and parents.

With the obvious limitations of the observational design of these studies, the general conclusion is that IFN- β is effective in the majority of patients, though about 30% of pediatric patients do not respond as expected, requiring more aggressive treatments²⁷ (see “Pediatric multiple sclerosis: Escalation and emerging treatments,” p. S103).

Data on adverse events have not been collected in a standardized fashion, and the definition of an adverse event differs across published studies, as well as the accuracy of detection. Flu-like symptoms have been reported in 8%–85% of children treated with interferon, myalgia in 5%–23%, headache in 8%–20%, gastrointestinal symptoms in 7%–10%, injection site reaction in 7%–75%, elevation of liver enzymes in 0%–38%, blood cell abnormalities in 2%–39%, and thyroid dysfunction in 1%–10%. Other rare adverse events have been reported in single cases (no more than 2 cases) and comprise menstrual disorders, depression, psychological disturbances, suicide attempt, arthritis, cartilage disorders, autoimmune disorders, serious infections, and malignancy.

There is limited information on the effect of IFN- β on body development. Data have been provided on 16 cases from a cohort of 52 pediatric patients with MS exposed to IFN- β treatment for a mean time of 43 months²⁸: in 10 girls who reached a mean age of 21.2 ± 5.0 years and in 6 boys who reached a mean age of 15.0 ± 2.5 years, weight and height resulted within the 10th–90th percentile of the normal population. Based on available data of scientific literature, there is no sign of a possible negative effect of IFN- β on body development.

A recent phase 4 multicenter study including 307 patients treated with IFN- β -1a 22/44 μg 3 times weekly confirmed the favorable safety profile of IFN- β as well as the reduction of relapse rate during the treatment phase.²² Rare adverse events (less than 2%) noted in this study included allergic reactions in 5 patients (1.6%), epilepsy and convulsive disorders in 5 (1.6%), thyroid dysfunction in 3 (1.0%), and autoimmune disorders, bone/cartilage disorders, and serious infections in 2 patients, respectively (0.7%). One child required omentectomy, classified under malignancy in Medical Dictionary for Regulatory Activities Query, and considered not related to IFN- β treatment by the treating physician.

Two studies evaluated the effect of GA in a small number of patients (21 cases): the clinical outcome

Table 1 Demographic and clinical findings of studies^a evaluating the results of interferon- β (IFN- β) and glatiramer acetate in pediatric patients with multiple sclerosis

	Waubant et al. ¹⁶	Mikaeloff et al. ¹⁷	Ghezzi et al. ²¹	Pohl et al. ¹⁹	Tenembaum and Segura ²⁰	Ghezzi et al. ²¹	Tenembaum et al. ²²	Banwell et al. ²³	Mikaeloff et al. ²⁴	Kornek et al. ²⁵	Ghezzi et al. ²¹
Drug	a	a + b + c	a	b	b	b + c	b	b	a + b + c	d	d
No. of cases	9	13	77	51	24	39	307	43	24	7	14
Age at treatment onset, y	12.7	15.5	13.4	14.6	12.7	14.1	14.3	13	15.4	16.6	14.0
Treatment duration, mo	17	12	54	22	44	60	24	29	66	24	75
Adverse events, %											
Flu-like	44	85	25	65	58	8	25	33	—	—	—
Myalgia	22	23	9	14	17	5	5	—	—	—	—
Headache	—	—	19.5	—	—	8	8	—	—	—	—
Gastrointestinal symptoms	—	—	—	10	—	7	—	—	—	—	—
Injection site reaction	11	15	6.5	71	75	18	28	21	—	57	14
Elevation of liver enzymes	—	7	5	35	33	0	38	19	—	—	—
Blood cell abnormalities	—	—	1.5	39	8	3	4.6	—	—	—	—
Thyroid dysfunction	—	—	10	—	—	—	1	—	—	—	—
Dyspnea, systemic reaction	—	—	—	—	—	—	—	—	—	14	7
Fatigue/asthenia	—	—	6.5	—	—	7	—	2	—	—	7
Results											
RR (pre/after)	—	—	2.5/0.4	1.9/0.8	1.7/0.04	3.2/0.9	—	—	—	—	2.9/0.3
EDSS	—	Stable	Stable	Stable	Stable	Stable	—	—	—	Stable	Stable
Treatment failure/discontinuation, %	44	25	26	—	—	64	—	25	—	—	—
Other endpoints	—	—	—	—	—	—	—	RR reduced by 50%	Less attacks, less disability	28% Relapse-free	—

Abbreviations: a = IFN- β -1a 30 μ g IM weekly; b = IFN- β -1a 22 or 44 μ g SC 3 times weekly; c = IFN- β -1b 250 mg every other day; d = Copaxone 20 mg IM daily; EDSS = Expanded Disability Status Scale; RR = relapse rate.

^aLimited to the last follow-up for studies with different time point observations.

was favorable in both studies, and no major adverse events have been recorded. However, acute hepatotoxicity confirmed by hepatic biopsy in an adolescent treated with GA has recently been reported.²⁹ Of note, this girl had been treated before with IFN- β -1a 44 mg and had developed elevation of liver enzymes, resulting in IFN- β -1a discontinuation and a switch to GA. Nevertheless, the exact causative mechanism of this adverse event remains to be elucidated.

RESULTS IN YOUNG CHILDREN VS ADOLESCENTS

Some studies have included children under the age of 10 years or 12 years, analyzing those subgroups separately: the clinical outcome was not different compared to patients with a higher age as well as the occurrence of adverse events; the only exception was increased rate of elevation of liver enzymes in the younger group of patients with MS in one study²³ (table 2).

Based on the results from a recently published study by Tenembaum et al.,²² the label of IFN- β -1a 22 or 44 μ g has been modified in the European Union as follows: “The results of this study suggest that the safety profile in children (2–11 years old) and in adolescents (12–17 years old) receiving Rebif 22 or 44 μ g subcutaneous 3 times per week is similar to that seen in adults. The safety and efficacy of Rebif in children below 2 years of age have not yet been established. Rebif should not be used in this age group.”

DMT IN CLINICAL PRACTICE

In recent years, 2 position papers have been published on the use of DMTs in the pediatric MS population.^{1,3} The European document suggested early use of DMTs to prevent relapses, accumulation of disability, and accumulation of brain damage, recommending careful clinical and MRI follow-up.³ Similarly, the International Pediatric Multiple Sclerosis Study Group consensus statement

Table 2 Adverse events in children compared to adolescents or to the whole cohort of patients with multiple sclerosis

Drug	Ghezzi et al. ²¹		Tenenbaum and Segura ²⁰		Ghezzi et al. ²¹		Tenenbaum et al. ²²		Banwell et al. ²³	
	a		b		b		b		c	
Age, y	<12	Whole cohort	<10	>10	<12	Whole cohort	<12	>12	<10	>10
No. of cases	9	77	8	16	5	39	52	255	8	35
Adverse events										
Flu-like	11	25	75	50	—	8	26.9	23.9	25	37
Myalgia	—	9	25	12.5	—	5	—	—	—	—
Headache	—	19.5	—	—	20	8	—	—	—	—
Gastrointestinal symptoms	—	—	—	—	—	7	—	—	—	—
Injection site reaction	11	6.5	50	87.5	20	18	21.2	29.0	25	20
Elevation of liver enzymes	11	5	37.5	31.2	—	0	15.4	14.1	—	—
Blood cell abnormalities	22	1.5	0	12.5	—	3	3.8	4.7	—	—
Thyroid dysfunction	—	10	—	—	—	—	1.9	0.8	62.5	22
Dyspnea, systemic reaction	—	—	—	—	—	—	1.9	1.6	—	—
Fatigue/asthenia	11	6.5	—	—	—	7	—	—	—	—

Abbreviations: a = IFN-β-1a 30 μg IM weekly; b = IFN-β-1a 22 or 44 μg SC 3 times weekly; c = IFN-β-1b 250 mg every other day.

recommends the use of first-line therapies as the standard of care for all pediatric patients with a diagnosis of MS.¹

The general approach is shown in the figure.

Pediatric patients with MS should start DMT treatment soon after diagnosis, with regular follow-up:

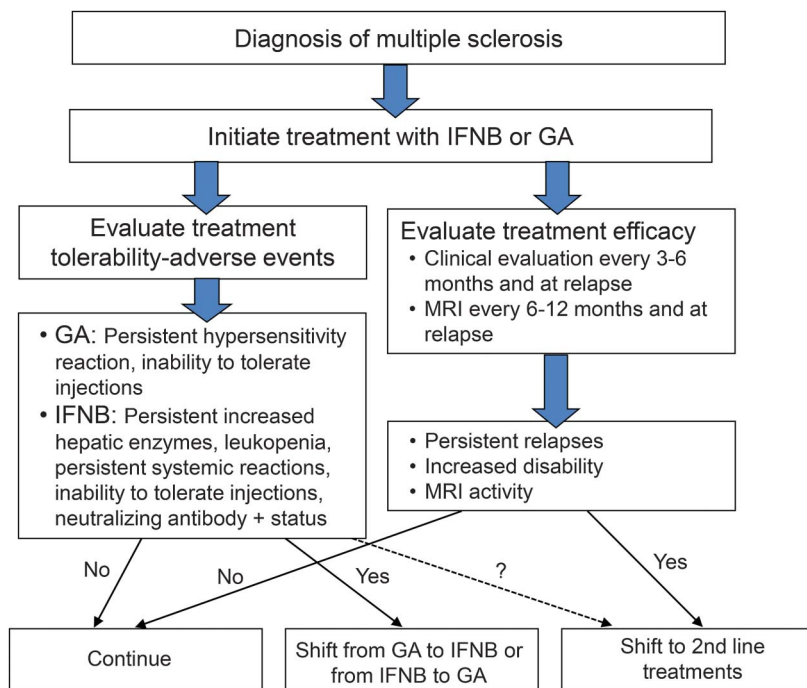
1. To assess clinical response with regular clinical evaluations (every 3–6 months, according to label/regulatory/local guidelines) and brain MRI every 6–12 months (according to label/regulatory/local guidelines)
2. To check the tolerability/safety profile (every 3–6 months, according to label/regulatory/local guidelines); periodic assessment of blood cell count, liver function, and thyroid and kidney function should be performed

There are no pharmacodynamic/pharmacokinetic studies of IFN-β and GA in pediatric MS. In general, it is recommended to initiate IFN-β therapy with 25%–50% of the adult dose. If well-tolerated, it is recommended to titrate up to full adult dose, especially for children over 12 years of age with a body weight more than 30 kg.

Adverse events should be appropriately managed: acetaminophen or ibuprofen before IFN-β injection or at appearance of flu-like symptoms reduce their frequency and severity. An educational program for patients and parents is also an important aspect when starting a DMT therapy, as they should be carefully informed on realistic expectations and management of adverse events, and trained on injection technique.

Patients treated with IFN-β can develop neutralizing antibodies resulting in a reduced biological activity of this medication and an increased risk of relapses^{30,31}; according to these recommendations, testing for the presence of neutralizing antibodies (NAbs), if available, should be performed in patients

Figure Diagram shows the main steps in the treatment of pediatric multiple sclerosis (MS)



It is suggested to start MS treatment with current first-line medications early. Patients with adverse events or poor tolerability can be offered to change the first-line therapy, switching to glatiramer acetate (GA) if previously treated with interferon-β (IFN-β) or vice versa. Switching to a second-line therapy can be considered for patients who do not adequately respond to current first-line therapies.

at 12 and 24 months of therapy or if there is evidence of breakthrough disease activity. Positive titers of NAb may be relevant to guide treatment decisions: if confirmed at repeated measurements with 3- to 6-month intervals, IFN- β should be discontinued.

Recent reports have described the occurrence of thrombotic microangiopathy in adults treated with IFN- β ³² as well as the association between glomerulonephritis and sarcoid-like lung disease with long-term IFN- β treatment.³³ Patients should be carefully monitored for safety evaluation and to discover possible rare adverse events: this issue is particularly important in pediatric patients, when children are being exposed to medications during key periods of growth and body development.

DISCUSSION Trials are ongoing evaluating the clinical outcome of pediatric patients with MS treated with fingolimod, dimethyl fumarate, and teriflunomide. If their effectiveness and safety in this age group is confirmed, new medications will be available in the future, with the advantage of oral administration. At present, IFN- β and GA continue to be the standard first-line treatments for pediatric patients with MS, as supported by observational studies and experts' consensus guidelines.

Clinicians should carefully follow-up children and adolescents with MS treated with DMT giving appropriate assistance, strengthening the adherence to therapy, managing adverse events properly, and switching treatment to other options in patients with inadequate or suboptimal response (see "Pediatric multiple sclerosis: Escalation and emerging treatments," p. S103).

AUTHOR CONTRIBUTIONS

Angelo Ghezzi designed the study, collected literature sources, analyzed and interpreted data of these studies, coordinated the group, and drafted and revised the manuscript. Maria Pia Amato, Teri Schreiner, Jutta Gärtner, and Naila Makhni helped draft, revise, and edit the manuscript for important intellectual content. Sylvia Tenembaum helped revise and edit the manuscript for important intellectual content.

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DISCLOSURE

A. Ghezzi received honoraria for speaking from Biogen-Idec, Merck-Serono, Novartis, Genzyme, Teva, and Allergan, and for consultancy from Merck-Serono, Teva, Novartis, and Biogen-Idec, and received support for participation in National and International Congresses from Schering, Biogen-Idec, Merck-Serono, Novartis, Genzyme, and Teva. M. Amato served on scientific advisory boards for and has received speaker honoraria and research support from Biogen Idec, Merck Serono, Bayer Schering Pharma, and Sanofi-aventis and serves on the editorial board of *BMC Neurology*. N. Makhani received fellowship funding from the Canadian Network of MS Clinics and receives research funding from the Dairy Farmers of Ontario and Race to Erase MS. Dr. Makhani is a site investigator for a clinical trial sponsored by Novartis. T. Schreiner received consulting fees from Biogen Idec, and participated in clinical research sponsored by Biogen Idec, Novartis Pharmaceuticals, MSDx, Adamas

Pharmaceuticals, and NIH. J. Gärtner received honoraria and consultancy fees from Bayer Vital, Biogen, Merck Serono, Teva, and Novartis and has received research grant support from Novartis and Biogen. S. Tenembaum served as an advisory board member or speaker for Merck Serono. Professional travel/accommodations expenses have been awarded to Dr. Tenembaum by Merck-Serono. She serves on a clinical trial advisory board for Genzyme-Sanofi. Go to Neurology.org for full disclosures.

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generates the question: Would this high exacerbation rate happen if patients were allowed to achieve remission with steroids without using MMF?

It was previously illustrated that among patients with MG who were treated with steroids, 80.2% (93/116) achieved remission/minimal manifestations status and only 18% (17/93) experienced an exacerbation afterward.² This clues in that the high exacerbation rate reported by Oskarsson et al. after discontinuing MMF may not reflect the natural disease activity but rather reflects MMF dependence, and that continuing MMF mainly treats the dependence. Both studies are limited by a lack of information on the prednisone dose required to maintain remission/minimal manifestations status (an important data point to determine whether MMF is effective).

Author Response: Björn Oskarsson, Sacramento; David M. Rocke, Davis; Karsten Dengel, Sacramento; David P. Richman, Davis, CA: We thank Dimachkie et al. for their interest in our article.¹ However, in opposition to Dimachkie et al., we would consider MG exacerbations after discontinuation of MMF as MG exacerbations rather than a novel MMF dependence

condition. Given this premise, patients with pharmacologically controlled MG seem a more appropriate control group compared to patients who had MG but sustain remission without pharmacologic treatment. We would suspect that patients without symptoms or treatment may have a less-active disease compared to a population requiring treatment. This last group is also rare in our clinic, further making such a comparison less meaningful.

The patients were selected on the basis of being on stable doses of prednisone (0–25 mg/d; see table 2)¹ and only MMF was varied. Our article does not address corticosteroid treatment of MG and we do not argue that corticosteroids are not an effective treatment of MG. The interest in treating MG with MMF stems primarily from MMF's more favorable side-effect profile.

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1. Oskarsson B, Rocke DM, Dengel K, Richman DP. Myasthenia gravis exacerbation after discontinuing mycophenolate: a single-center cohort study. *Neurology* 2016;86:1159–1163.
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CORRECTIONS

Neurofilament light chain level is a weak risk factor for the development of MS

In the article "Neurofilament light chain level is a weak risk factor for the development of MS" by G. Arrambide et al.,¹ there is an error in figure 2. In panel C, the p value should read " $p < 0.0001$ " rather than " $p, 0.0001$ " as originally published. The editorial staff regrets the error.

REFERENCE

1. Arrambide G, Espejo C, Eixarch H, et al. Neurofilament light chain level is a weak risk factor for the development of MS. *Neurology* 2016;87:1076–1084.

Pediatric multiple sclerosis: Conventional first-line treatment and general management

In the article "Pediatric multiple sclerosis: Conventional first-line treatment and general management" by A. Ghezzi et al.,¹ there is an error in the fourth author's name, which should have read "Teri Schreiner" rather than "Teri Shreiner" as originally published. The authors regret the error.

REFERENCE

1. Ghezzi A, Amato MP, Makhani N, et al. Pediatric multiple sclerosis: conventional first-line treatment and general management. *Neurology* 2016;87(suppl 2):S97–S102.

Author disclosures are available upon request (journal@neurology.org).