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Subcutaneous interferon β-1a in pediatric patients with multiple sclerosis: Regional differences in clinical features, disease management, and treatment outcomes in an international retrospective study

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ABSTRACT

Background: To further understand management of pediatric patients with multiple sclerosis (MS), we examined disease features, clinical practice patterns, and response to treatment in the United States (US) and seven other countries ('rest of World'; ROW).
Methods: Anonymized data, recorded as part of routine clinical practice, were obtained from medical records (1997–2009) of study participants (who received subcutaneous interferon β-1a before age 18 years) from the US and ROW. Samples were stratified by age (preadolescents [<12 years] and adolescents [12–17 years]).
Results: US adolescents had a higher mean body mass index versus ROW adolescents (BMI; 27.2 versus 22.5 kg/m^2), started disease-modifying therapy (DMT) earlier after the first relapse, were more likely to have received a DMT before initiating subcutaneous interferon β-1a, had a higher relapse rate, and were more likely to switch from subcutaneous interferon β-1a to another DMT before the end of the observation period.
Conclusions: This retrospective analysis of a multinational sample of pediatric MS patients who received subcutaneous interferon β-1a found that those from the US had higher BMI, relapsed more frequently, and were managed differently, compared with ROW patients. Future prospective studies are needed to confirm these observations and ascertain their clinical significance.

1. Introduction

There is international consensus on the importance of initiating disease-modifying therapy (DMT) in children and adolescents with multiple sclerosis (MS), and on the need for collaborative prospective research [1]. Children and adolescents with MS represent an understudied subgroup, largely due to the low frequency of MS in this age group. The incidence of MS in children and adolescents is estimated to be 0.18 to 0.51 per 100,000 [2], compared with 3.6 and 2.0 per 100,000 in women and men, respectively, as reported in one systematic review [3]. In recent years, the recognition of pediatric MS has grown and data have been gathered on the demographic and clinical features of this population from different regions of the world.

Still, it remains unclear how pediatric patients with MS respond to DMTs and whether regional differences impact the management of MS with DMTs. Small studies (most involving 50 or fewer participants) have demonstrated that baseline relapse rates decrease after treatment with DMTs [4–12]. Recently, our group, the REPLAY study investigators, completed the largest reported retrospective analysis of treatment experience with subcutaneous (sc) interferon (IFN) β-1a in pediatric patients with MS. Based on the review of medical records from 307 pediatric patients (298 of whom had a final diagnosis of MS) enrolled from eight countries, we found that adult doses of sc IFN β-1a (44 and 22 μg three times weekly [tiw]) were well tolerated and associated

Abbreviations: ARR, annualized relapse rate; BMI, body mass index; DMD, disease-modifying therapy; DMT, disease-modifying therapy; IFN, interferon; ME, medical events; MS, multiple sclerosis; ROW, rest of the world; SD, standard deviation; US, United States.

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with a reduction in relapse rates compared with rates before treatment [12]. Here we report data from post hoc analyses comparing REPLAY participants enrolled from the United States (US) with those enrolled from Italy, Russia, Argentina, France, Canada, Tunisia, and Venezuela, analyzed together as the 'rest of the world' (ROW) group. These analyses examined selected baseline clinical features, treatment practices, and outcomes between the US and ROW, where healthcare environments vary, to determine whether regional differences impact the management of MS with DMTs.

2. Methods

2.1. Study design

International Review Board or Independent Ethics Committee approval of the protocol was obtained from each participating site. Details of the study methodology have been described (NCT01207648) [12]. All patients who had received ≥1 injection of sc IFN β-1a for demyelinating events before the age of 18 years were eligible for inclusion, and treatment with sc IFN β-1a must have been initiated before June 2009 (allowing at least 6 months of observation for each patient). The aim was to assess all eligible patients at each center. The final analyses were limited to patients who received a confirmed diagnosis of MS only.

Data were collected from the medical records of patients evaluated between 1997 and 2009. All analyzed information was recorded as part of routine clinical practice. The observation period for an individual patient began with the first medical record available on site and ended on 31 December 2009, or when the patient was lost to follow-up, whichever occurred first.

2.2. Outcomes

Baseline demographics, clinical characteristics, and treatment patterns and outcomes of patients from the US and ROW were compared. Prespecified medical events (MEs) occurring after the initiation of sc IFN β-1a treatment (based on the known safety profile of sc IFN β-1a [13,14]) were recorded. Clinical relapses were defined as the emergence of new neurological symptoms and signs that occurred ≥30 days after the last event and persisted for ≥24 h in the absence of intercurrent illness.

2.3. Statistical analysis

Efficacy and safety outcomes were assessed. All comparisons were exploratory and descriptive. Interpretation of results was based on point estimates and their corresponding 95% confidence interval. Mean and 95% CI were calculated using the Poisson model to provide adjusted means (adjusted for baseline characteristics [region and age]). All statistical analyses were performed using SAS version 9.1 (or higher) software (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Total sample of patients with pediatric MS

A total of 298 patients were confirmed to have MS and were prescribed sc IFN β-1a (44 or 22 μg tiw). Patients enrolled were from the US (n = 131 [44.0%]) and ROW (n = 167 [56.0%]); the latter comprised patients from Italy (n = 47 [15.8%]), Russia (n = 38 [12.8%]), Argentina (n = 33 [11.1%]), France (n = 22 [7.4%]), Canada (n = 21 [7.0%]), Tunisia (n = 3 [1.0%]), and Venezuela (n = 3 [1.0%]).

3.2. Baseline characteristics

Overall, 61.7% (184/298) of patients who had received an MS diagnosis were female. The mean (standard deviation) age was 12.3 (3.4) years at the first clinical demyelinating event, 13.3 (3.1) years at MS diagnosis, and 14.1 (2.9) years at initiation of sc IFN β-1a treatment. A total of 96 (37.4%) patients had a monofocal presentation, 171 (57.4%) were hospitalized for the first clinical demyelinating event, 177 (59.4%) received steroid treatment, and 297 (99.7%) had an initial relapsing–remitting MS course.

3.2.1. Regional contrasts in demographic and clinical characteristics

3.2.1.1. Age. As a result of a lower proportion of children <12 years among those enrolled from US sites compared with the ROW (15/131 [11%] vs 35/167 [21%]), all analyses were stratified by age group (preadolescent [<12 years] and adolescent [12–17 years]).

3.2.1.2. Demographics and clinical characteristics. Patient demographics and clinical characteristics by region are presented in Table 1. Adolescents (12–17 years) from the ROW had a disease duration prior to sc IFN β-1a initiation that was more than twice that of adolescents from the US (median days [range]: 164.5 [1, 3111] vs 62.0 [−116, 3638]), and lower Expanded Disability Status Scale (EDSS) score at sc IFN β-1a initiation (median [range]: 1.50 [0.0, 6.0] vs 2.00 [0.0, 8.0], Table 1). Preadolescents (<12 years) from the ROW had fewer clinical attacks prior to sc IFN β-1a initiation than those from the US (median [range]: 2.0 [1, 9] vs 3.0 [1, 7]). Interesting patterns emerged from analyses of body mass index (BMI) where these data were available. The proportion of missing data among adolescents was 59% and 75% from the US and ROW, respectively (Table 1). Fortunately, there were no differences in demographic features between participants with BMI data and those with BMI data missing from their records. While there was little difference in BMI for the preadolescent groups, there were striking differences in the mean and median BMI among adolescents from the US and the ROW. Adolescents from the US had mean and median values that were at least 17% higher than those of the ROW (Table 1).

3.2.1.3. Clinical outcomes. The annualized relapse rate (ARR) prior to initiation of DMT was comparable in the US and ROW for both age groups (mean: 1.9 and 2.1 [<12 years] and 1.7 and 1.8 [12–17 years], respectively; Fig. 1). However, preadolescents from both regions had slightly higher baseline ARR compared with adolescents.

The ARR decreased following sc IFN β-1a treatment in preadolescents and adolescents from both the US and ROW (Fig. 1). However, ARRs during sc IFN β-1a therapy were higher in the US for both age groups, compared with in the ROW. Both age groups from the US had a higher ARR relative to the ROW during the period between treatment termination and the end of the observation period. The median time to first relapse after treatment initiation was shorter in the US (14.2 months) than in the ROW (27.2 months).

3.2.1.4. On-study treatment patterns. Demographic and clinical features are shown in Table 2. Adolescent patients in the US had a markedly shorter median interval from the first clinical demyelinating event to initiating DMT, compared with adolescent patients in the ROW (Table 2). Patients from the US had a greater likelihood of receiving a different DMT preceding initiation of sc IFN β-1a. For example, 60.0% of preadolescents and 29.3% of adolescents in the US received a prior DMT before starting treatment with sc IFN β-1a. In contrast, only 13–14% of preadolescents and adolescents from the ROW received a DMT prior to sc IFN β-1a treatment.

3.2.1.5. Prescribing patterns for sc IFN β-1a. A greater proportion of patients in the US received 44 μg tiw as their targeted prescribed dosage of sc IFN β-1a, compared with patients from the ROW (Table 3). Patients in the US also had a shorter time on sc IFN β-1a treatment, were less likely to be receiving ongoing sc IFN β-1a therapy at study end, and were more likely to have switched to another DMT during the study period.

Table 1
Baseline characteristics and demographics among preadolescents and adolescents with multiple sclerosis, by region.

Characteristic	Preadolescents (<12 years)		Adolescents (12–17 years)	
	US (n = 15)	ROW (n = 35)	US (n = 116)	ROW (n = 132)
Female	5 (33.3)	15 (42.9)	76 (65.5)	88 (66.7)
Age for those with BMI data, years				
n (missing)	5 (10)	17 (18)	48 (68)	33 (99)
Mean (SD)	8.2 (2.8)	8.3 (3.0)	15.2 (1.5)	14.9 (1.4)
Median (range)	9.0 (4, 11)	10.0 (3, 11)	15.0 (12, 17)	15.0 (12, 17)
BMI, kg/m^2				
Mean (SD)	18.8 (3.8)	18.4 (2.7)	27.2 (7.5)	22.5 (3.9)
Median (range)	16.8 (15.6, 23.4)	19.2 (13.6, 22.0)	26.4 (17.3, 51.3)	22.6 (15.6, 34.2)
Monofocal	2 (15.4)	12 (34.3)	14 (17.5)	68 (52.7)
Multifocal	11 (84.6)	23 (65.7)	66 (82.5)	61 (47.3)
Disease duration pre sc IFN β-1a, days				
n (missing)	15 (0)	35 (0)	116 (0)	132 (0)
Mean (SD)	176.6 (290.5)	209.5 (268.2)	196.9 (446.2)	410.0 (597.7)
Median (range)	150.0 (−395, 731)	137.0 (7, 1370)	62.0 (−116, 3638)	164.5 (1, 3111)
EDSS at sc IFN β-1a initiation				
n (missing)	9 (6)	34 (1)	90 (26)	127 (5)
Mean (SD)	1.56 (1.04)	2.29 (1.23)	1.97 (1.47)	1.69 (1.07)
Median (range)	2.00 (0.0, 3.0)	2.00 (0.0, 6.0)	2.00 (0.0, 8.0)	1.50 (0.0, 6.0)
Number of clinical attacks prior to sc IFN β-1a initiation				
n (missing)	15 (0)	35 (0)	116 (0)	132 (0)
Mean (SD)	3.5 (1.9)	2.7 (1.8)	2.7 (2.4)	2.7 (1.7)
Median (range)	3.0 (1, 7)	2.0 (1, 9)	2.0 (1, 22)	2.0 (1, 14)

BMI, body mass index; EDSS, Expanded Disability Status Scale; IFN β-1a, interferon β-1a; ROW, rest of the world; sc, subcutaneous; SD, standard deviation; US, United States.

3.3. Prespecified medical events

Minor differences in the overall occurrence of prespecified MEs were observed between the US and ROW (Table 4). The most commonly reported prespecified MEs in the US were injection-site reactions, followed by 'flu-like' symptoms. In contrast, 'flu-like' symptoms were more common than injection-site reactions in the ROW.

4. Discussion

Across the countries studied, the main conclusions from the REPLAY study [12] are still applicable. Specifically, regardless of region, sc IFN β-1a treatment was well tolerated in preadolescents and adolescents with MS. Treatment was also associated with a reduction in clinical relapses compared with before treatment.

Compared with the ROW, there was a lower proportion of preadolescent patients (aged <12 years) in the US. This could at least be partly explained by site-specific practice patterns.

While there were limited available data, BMI was noticeably higher among adolescents from the US, an observation that is consistent with the current epidemic of childhood and teenage obesity in the US [15]. In 2007, 16.4% of US children were obese and 31.6% were overweight, with substantial geographic variation [16]. Furthermore, a systematic review showed that adolescent obesity was higher in the US than other countries studied [17]. Childhood obesity has been associated with an increased risk of pediatric MS [18]. In the current study, the analyses on BMI were limited because of missing data. However, clinical and demographic features of those missing BMI data and those with BMI data did not differ, and the extent of missing data is comparable across regions. Future prospective international research should further examine the association between global region, BMI, and pediatric MS.

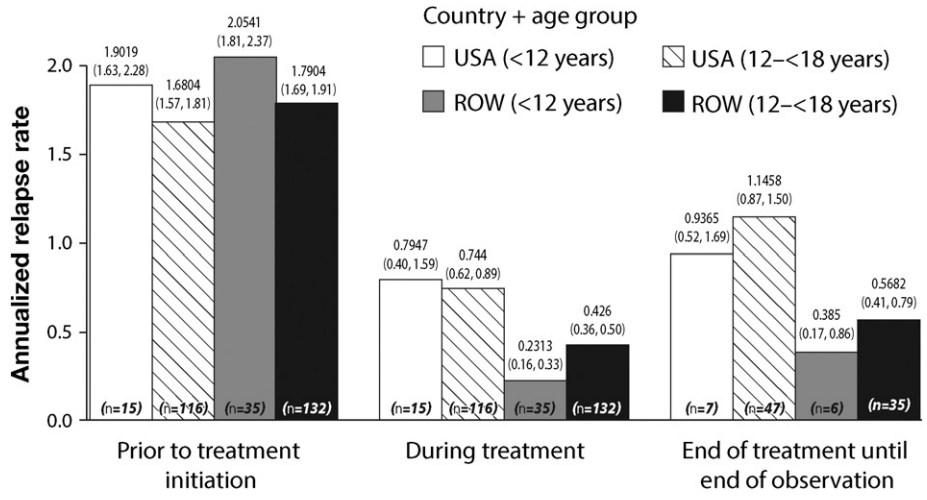

Fig. 1. Medically confirmed clinical relapses prior to, during, and after termination of subcutaneous interferon β-1a treatment in patients with multiple sclerosis by country and age groups. ROW, rest of the world. Values presented are mean (95% CI).

Table 2
Clinical management patterns for preadolescents and adolescents with multiple sclerosis at baseline, by region.

Characteristic	Preadolescents (<12 years)		Adolescents (12–17 years)	
	US (n = 15)	ROW (n = 35)	US (n = 116)	ROW (n = 132)
Time from first demyelinating event to first DMT, years				
Mean (SD)	1.53 (1.57)	0.65 (0.52)	0.91 (1.10)	1.75 (1.48)
Median (range)	0.77 (0.1, 4.9)	0.67 (−0.1, 1.4)	0.64 (0.1, 5.7)	1.15 (0.4, 6.0)
Received >1 DMT prior to IFN	9 (60.0)	5 (14.3)	34 (29.3)	17 (12.9)
Hospitalized for initial relapse	13 (86.7)	27 (77.1)	54 (46.6)	77 (58.3)
Treated with steroids for initial relapse	13 (86.7)	28 (80.0)	60 (51.7)	76 (57.6)

Data presented as n (%) unless specified otherwise.
DMT, disease-modifying therapy; IFN, interferon; ROW, rest of the world; SD, standard deviation.

Interesting differences were also found between prescribing patterns in the US and the ROW. Patients in the US had a higher frequency of other DMT use prior to initiation of sc IFN β-1a, and stayed on sc IFN β-1a treatment for a shorter time. The explanation for the higher frequency of other DMT use prior to initiation sc IFN 1a in the US compared to other countries is unknown. One possibility is that since low-dose low-frequency IFN β-1a had the greatest market share during this period in the US and it could have been preferentially given to younger patients. Furthermore, sc IFN β-1a was first available in Europe in 1998, but was not available in the US until 2002 so may have not been used as often. Further research is needed to determine whether these differences can be explained by other differences in prescribing habits and access to healthcare resources among countries.

On-treatment relapses occurred more frequently among patients from the US. It is unclear whether this represents varying disease patterns due to different racial and ethnic composition or differences in access to healthcare resources, leading to increased reporting of relapses. Different availability of other treatments is likely to have contributed to the increased switching rate among patients from the US; however, the relative influence of disease factors versus healthcare practice factors cannot be determined from these data.

While sc IFN β-1a was well tolerated overall, there was a higher incidence of injection-site reactions among patients from the US. One possible explanation is that different formulations of sc IFN β-1a were used across the countries in this analysis. From 2007, a new serum-free formulation was gradually introduced in Europe and other regions, designed to reduce immunogenicity and improve local tolerability of the treatment. This formulation has been associated with an incidence of injection-site reactions approximately threefold lower than that found in historical studies involving the original formulation [12]. The new formulation has not been approved in the US, and therefore US patients in the present study were treated with the original, serum-containing formulation. The transition between formulations may also have contributed to the higher incidence of 'flu-like' symptoms in the ROW population because, similarly to when initiating IFN, a transient increase in 'flu-like' symptoms is possible when patients switch to another formulation [11,12].

The main limitation of this study is its retrospective nature. Some of the variables examined in this post hoc analysis, such as BMI, were outside the primary focus of the original investigation, and therefore there were high rates of missing data. EDSS score at the time of attack was unfortunately not measured so we are unable to speculate on the impact of relapse severity. Moreover, as this was not a clinical trial, there were no preset algorithms for the evaluation of relapses, treatment decisions, and subsequent management. However, the observed differences in practice patterns and some clinical features can generate further hypothesis testing in prospective studies. To minimize the potential selection bias inherent to the retrospective patient ascertainment, the study sought to assess all pediatric patients who commenced treatment with sc IFN β-1a prior to 30 June 2009 in the participating centers. However, patients from different centers had varying exposure to sc IFN β-1a and varying follow-up times, and confounding factors included exposure to other medications, co-morbidities, gender, and age at the time of sc IFN β-1a initiation. In addition, biases could also have been introduced by the site, country, or region due to differences in treatment practices.

Taken together, the findings presented here show that, compared with the ROW, adolescents with MS from the US have a higher BMI and appear to be managed differently relative to their ROW counterparts: a greater variety of DMTs are prescribed, treatment is started more quickly from the time of diagnosis, and there is a greater tendency to switch therapies. Future studies should confirm whether patients from the US have higher BMI and how this may relate to other clinical features. Prospective studies could identify any regional differences in disease course and ascertain how demographic features may be associated with clinical outcomes. Healthcare practices worldwide should also be compared and examined for their effects on outcomes.

Table 3
Dose and duration of sc IFN β-1a treatment and treatment status at the end of the observation period by region.

Variable	Preadolescents (<12 years)		Adolescents (12–17 years)	
	US (n = 15)	ROW (n = 35)	US (n = 116)	ROW (n = 132)
First treatment dose				
44 μg tiw	8 (53.3)	1 (2.9)	98 (86.7)	32 (25.0)
22 μg tiw	4 (26.7)	28 (80.0)	10 (8.8)	74 (57.8)
Other dosage[a]	3 (20.0)	6 (17.1)	5 (4.4)	22 (17.2)
Time on treatment (years)				
Mean (SD)	0.67 (0.76)	3.95 (3.44)	1.46 (1.04)	2.45 (2.13)
Median (range)	0.42 (0.0, 2.3)	3.28 (0.1, 12.5)	1.16 (0.0, 4.4)	1.52 (0.0, 7.8)
Status of sc IFN β-1a treatment at end of observation period				
Ongoing treatment	8 (53.3)	29 (82.9)	69 (59.5)	97 (73.5)
Switched to other DMT	5 (33.3)	1 (2.9)	33 (28.4)	21 (15.9)
Discontinued all treatment	2 (13.3)	5 (14.3)	14 (12.1)	14 (10.6)

Data presented as n (%) unless specified otherwise.
DMD, disease-modifying therapy; IFN, interferon; ROW, rest of the world; sc, subcutaneous; SD, standard deviation; tiw, three times weekly.
[a] Data from some patients are not included because these patients had received an initial dose other than 44 or 22 μg tiw.

Table 4
Incidence of prespecified medical events by region.

Region	Preadolescents (<12 years)		Adolescents (12–17 years)	
	US (n = 15)	ROW (n = 35)	US (n = 116)	ROW (n = 132)
Patients with at least one prespecified event	5 (33.3)	24 (68.6)	65 (56.0)	70 (53.0)
Injection-site reactions	3 (20.0)	6 (17.1)	44 (37.9)	29 (22.0)
'Flu-like' symptoms	0	14 (40.0)	24 (20.7)	36 (27.3)
Hepatic disorders	3 (20.0)	5 (14.3)	12 (10.3)	24 (18.2)
Blood cell abnormalities (e.g. thrombocytopenia, leukopenia, anemia)	1 (6.7)	1 (2.9)	2 (1.7)	10 (7.6)
Allergic reactions (e.g. rash, urticaria and anaphylaxis)	0	1 (2.9)	3 (2.6)	0
Epilepsy and convulsive disorders	0	1 (2.9)	2 (1.7)	1 (0.8)
Thyroid dysfunction	0	1 (2.9)	0	2 (1.5)
Autoimmune diseases	0	0	2 (1.7)	0
Bone/epiphyseal and cartilage disorders	0	1 (2.9)	0	1 (0.8)
Serious infections	0	0	2 (1.7)	0
Malignancies	0	1 (2.9)	0	0

ROW, rest of the world.

Conflict of interest

LB Krupp has received personal compensation for activities as a speaker, consultant and/or participant on an advisory board from Biogen Idec, Novartis Pharmaceuticals, Teva Neurosciences, and Multicell; royalty or license fees from ER Squibb & Sons, Avenir, Johnson & Johnson, and Osmotica; grant support from the National Multiple Sclerosis Society, National Institutes of Health, and the Department of Defense; and research support from Novartis, Biogen Idec, Celgene Corporation, and Genentech. She has also received support from the Lourie Foundation, Slomo and Cindy Silvian Foundation, and the Multiple Sclerosis Foundation.

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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 clinical trial advisory boards for Genzyme-Sanofi.

L Chen is an employee of EMD Serono, Inc.

E Aycardi was an employee of EMD Serono, Inc. at the time of manuscript preparation.

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References

[1] T. Chitnis, S. Tenembaum, B. Banwell, L. Krupp, D. Pohl, K. Rostasy, E.A. Yeh, O. Bykova, E. Wassmer, M. Tardieu, A. Kornberg, A. Ghezzi, Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis, Mult. Scler. 18 (2012) 116–127.
[2] T. Chitnis, M. Tardieu, M.P. Amato, B. Banwell, A. Bar-Or, A. Ghezzi, A. Kornberg, L.B. Krupp, D. Pohl, K. Rostasy, S. Tenembaum, E. Waubant, E. Wassmer, International Pediatric MS Study Group Clinical Trials Summit: meeting report, Neurology 80 (2013) 1161–1168.
[3] A. Alonso, M.A. Hernan, Temporal trends in the incidence of multiple sclerosis: a systematic review, Neurology 71 (2008) 129–135.
[4] A.B. Adams, W.R. Tyor, K.R. Holden, Interferon beta-1b and childhood multiple sclerosis, Pediatr. Neurol. 21 (1999) 481–483.
[5] B. Banwell, A.T. Reder, L. Krupp, S. Tenembaum, M. Eraksoy, B. Alexey, D. Pohl, M. Freedman, L. Schelensky, I. Antonijevic, Safety and tolerability of interferon beta-1b in pediatric multiple sclerosis, Neurology 66 (2006) 472–476.
[6] L.J. Etheridge, D.W. Beverley, C. Ferrie, E. McManus, The use of interferon beta in relapsing–remitting multiple sclerosis, Arch. Dis. Child. 89 (2004) 789–791.
[7] A. Ghezzi, M.P. Amato, P. Annovazzi, M. Capobianco, P. Gallo, M.L. La Mantia, M.G. Marrosu, V. Martinelli, N. Milani, L. Moiola, F. Patti, C. Pozzilli, M. Trojano, M. Zaffaroni, G. Comi, Long-term results of immunomodulatory treatment in children and adolescents with multiple sclerosis: the Italian experience, Neurol. Sci. 30 (2009) 193–199.

[8] Y. Mikaeloff, T. Moreau, M. Debouverie, J. Pelletier, C. Lebrun, O. Gout, J.M. Pedespan, H.C. Van, P. Vermersch, G. Ponsot, Interferon-beta treatment in patients with childhood-onset multiple sclerosis, J. Pediatr. 139 (2001) 443–446.
[9] Y. Mikaeloff, G. Caridade, M. Tardieu, S. Suissa, Effectiveness of early beta interferon on the first attack after confirmed multiple sclerosis: a comparative cohort study, Eur. J. Paediatr. Neurol. 12 (2008) 205–209.
[10] I. Pirko, N.L. Kuntz, M. Patterson, B.M. Keegan, B.G. Weinshenker, M. Rodriguez, Contrasting effects of IFNbeta and IVIG in children with central and peripheral demyelination, Neurology 60 (2003) 1697–1699.
[11] D. Pohl, K. Rostasy, J. Gartner, F. Hanefeld, Treatment of early onset multiple sclerosis with subcutaneous interferon beta-1a, Neurology 64 (2005) 888–890.
[12] S.N. Tenembaum, B. Banwell, D. Pohl, L.B. Krupp, A. Boyko, M. Meinel, L. Lehr, S. Rocak, E. Verdun di Cantogno, M. Stammoraga, A. Ghezzi, on behalf of the REPLAY Study Group, Subcutaneous interferon beta-1a in pediatric multiple sclerosis: a retrospective study, J. Child Neurol. 28 (2013) 849–856.
[13] G. Comi, N. De Stefano, M.S. Freedman, F. Barkhof, C.H. Polman, B. Uitdehaag, F. Casset-Semanaz, B. Hennessy, S. Rocak, B. Stubinski, L. Kappos, Comparison of two dosing frequencies of subcutaneous interferon beta-1a in patients with a first clinical demyelinating event suggestive of multiple sclerosis (REFLEX): a phase 3 randomised controlled trial, Lancet Neurol. 11 (2012) 33–41.
[14] PRISMS Study Group, Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis, Lancet 352 (1998) 1498–1504.
[15] Y. Wang, M.A. Beydoun, The obesity epidemic in the United States–gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis, Epidemiol. Rev. 29 (2007) 6–28.
[16] G.K. Singh, M.D. Kogan, P.C. van Dyck, Changes in state-specific childhood obesity and overweight prevalence in the United States from 2003 to 2007, Arch. Pediatr. Adolesc. Med. 164 (2010) 598–607.
[17] M. Bibiloni Mdel, A. Pons, J.A. Tur, Prevalence of overweight and obesity in adolescents: a systematic review, ISRN Obes. 2013 (2013) 392747.
[18] A. Langer-Gould, S.M. Brara, B.E. Beaber, C. Koebnick, Childhood obesity and risk of pediatric multiple sclerosis and clinically isolated syndrome, Neurology 80 (2013) 548–552.