SAGE Open Medicine
Volume 11: 1–8

DOI: 10.1177/20503121231171996
journals.sagepub.com/home/smo
Sage

Narrative review based on fingolimod therapy in pediatric MS

Bilge Piri Cinar[1], Bahadır Konuskan[2], Banu Anlar[3] and Serkan Ozakbas[4]

Abstract

The course of pediatric-onset multiple sclerosis and adult multiple sclerosis shows some clinical differences. The rate of having a second attack after the first clinical event is 80% in children and around 45% in adults but the time to the second event is similar in all age groups. The pediatric group usually has a more aggressive onset than adults. On the other hand, a higher rate of complete recovery is observed in pediatric-onset multiple sclerosis after the first clinical event compared to the adult group. Despite a highly active initial disease course, pediatric-onset multiple sclerosis patients show a slower increase in disability than patients with adult-onset disease. This is thought to be due to greater remyelination capacity and plasticity of the developing brain. The management of pediatric-onset multiple sclerosis includes safety issues as well as effective disease control. In the pediatric-onset multiple sclerosis group, similar to adult multiple sclerosis, injectable treatments have been used for many years with reasonable efficacy and safety. Since 2011, oral treatments and then infusion treatments have been approved and used effectively in adult multiple sclerosis and have gradually entered clinical use in the pediatric-onset multiple sclerosis group. However, clinical trials are fewer, smaller, and include shorter follow-up due to the much lower prevalence of pediatric-onset multiple sclerosis than adult multiple sclerosis. This is particularly important in the era of recent disease-modifying treatments. This review of the literature presents existing data on the safety and efficacy of fingolimod, pointing to a relatively favorable profile.

Keywords

POMS, fingolimod, treatment, effectiveness, safety

Date received: 16 June 2022; accepted: 10 April 2023

Introduction

Multiple sclerosis (MS) is a chronic autoimmune neurodegenerative disease where demyelination and axonal loss in the central nervous system (CNS) play a role in the pathogenesis. Often presenting attacks and remissions, its course also includes an insidious progression. In about 5%–10% of individuals with MS, the disease has an onset before the age of 18 years.[1–4] Looking from another perspective, 15%–45% of those who experience a demyelinating event in childhood are diagnosed with MS.[5] The incidence of pediatric-onset MS (POMS) in the general population was shown as 0.64/100.000 and 0.09/100.000 for <10 years, and 2.64/100.000 for the population aged 14–15 years.[6] The prevalence of MS before puberty is close to equal between girls and boys, while the female predominance observed in adult-onset MS (AOMS) is also observed in POMS starting after puberty.[7–9]

CNS demyelination presents clinically with optic neuritis, brainstem syndrome, transverse myelitis, or supratentorial findings for all age groups. In the first demyelinating event, the onset may be in one or multiple regions. The most important limiting factor in the very young POMS group (<10 years) is the pediatric patient's inability to distinguish or fully express complaints such as sensory symptoms, blurred vision, or double vision. This limiting effect only

[1]Samsun University, Samsun, Turkey
[2]University of Health Sciences Turkey, Etlik City Hospital, Ankara, Turkey
[3]Hacettepe University, Ankara, Turkey
[4]Dokuz Eylul University, Izmir, Turkey

Corresponding author:
Bilge Piri Cinar, Neurology Department, School of Medicine, Samsun University, Samsun, Turkey.
Email: bilge.cinarpiri@gmail.com

applies to the very young age group (<10 years), but when it is combined with the presentation with encephalopathy and seizures more frequently than the adult group, there is more than one difficulty in diagnosing MS in the pediatric group.[9]

The course of POMS and adult MS shows some clinical differences. The rate of having a second attack after the first clinical event—clinically isolated syndrome—is approximately 80% in children and around 45% in adults,[10–13] but the time to the second event is similar in all age groups. POMS usually has a more aggressive onset than in adults. In addition, complete recovery after the first clinical event is more common in POMS patients than in the adult group (88.6% and 74.9%, respectively).[8,14] It should be noted that the majority of the publications mentioned here are from northern European and American countries and may contain regional differences depending on environmental and genetic factors.

Comparisons of POMS and AOMS show various results. The annual number of attacks is described as similar, or higher in POMS.[9,11,15–17] While the frequency of relapsing-remitting MS (RRMS) is over 95% in the POMS group, 85% of the patients in the AOMS group are defined as RRMS.[1,16] Progressive onset is seen in only 1%–3% of patients in the POMS group, compared to about 10% in adults.[9,17] In a study conducted with 186 POMS patients, a secondary progressive course was found in 5.38% of the study group.[18] In addition, the transition period to secondary progressive MS in POMS was 10 years longer than in adults.[19] Again, in connection with this, the time to reach the Extended Disease Status Scale (EDSS) 4 was found to be significantly longer in the POMS group than in the adult group (31 and 24.5 years, respectively).[8] However, in a disease that starts at a much earlier age and lasts for a relatively long time, it is predicted that the turning point of disability will naturally be reached earlier in POMS.[20,21] Despite a highly active disease course at baseline in POMS, they show a slower increase in disability than patients with adult-onset disease. This is thought to be due to greater plasticity of the developing brain.[22] The rate of cognitive impairment seen in adult-onset MS patients and POMS is similar but on a large range as 30%–75%.[23–25] Cognitive areas affected in the POMS group are information processing speed, working memory, visual perceptual learning and memory, executive vision and attention, and resemble AOMS. However, unlike adults, difficulties in perceiving and expressing language can be seen in POMS.[25]

Compensation mechanisms and plasticity in the child's brain are different compared to adults, and the volume of gray and white matter in the brain continues to change regionally throughout childhood.[26–28] In children diagnosed with RRMS, there is a marked decrease in total brain volume, especially gray matter and thalamus, and this effect has been shown to persist throughout adolescence.[29] This can be explained by neurodegeneration in addition to the underlying active and chronic inflammation. On the other hand, brain development can be negatively affected even in acute disseminated encephalomyelitis, which often presents with a single attack in childhood.[30] These data show the importance of making an early diagnosis of MS and starting an effective treatment in childhood.

The increase in the incidence and diagnosis of POMS can be evaluated as a result of the correct analysis of the data obtained for many years. This review aimed to emphasize the place of fingolimod in the treatment management of the subgroup, which may have an aggressive course, in individuals with POMS who occasionally have difficulties in the treatment management as well as the difficulties in the diagnosis process.

Search methods

The search strategy in the Medline/PubMed database was (“Multiple Sclerosis and “pediatric Multiple Sclerosis”[Title/Abstract] and “fingolimod and “Treatment”[Title/Abstract]). In all, 84 articles were found when searched in PubMed with these keywords. Original articles with high level of evidence related to POMS treatment, articles containing case series with close designs, and articles containing real-life data were included in the review. Also phase 3 studies of fingolimod were included in the review. Two reviewers independently scanned and selected abstracts, and fully read all potentially eligible articles. Disputes were resolved through a discussion with a third reviewer until consensus was reached. For data extraction and management, two reviewers evaluated all articles independently and excluded non-relevant ones, resulting in 60 articles included.

Treatments in pediatric-onset multiple sclerosis

Although the etiopathogenesis of MS is basically similar in POMS and AOMS, age is an important variable. Response to disease-modifying drugs (DMDs) can be expected to be the same (or better) in POMS and AOMS when MS is associated with higher inflammatory activity and better ability to compensate for brain injury in younger individuals.[31] There is a slight difference in annual relapse rate (ARR) between boys and girls. Pre-treatment ARR is reported to be higher in females and post-treatment reduction in ARR was significantly more noticeable in males.[32]

There is not enough information to establish a treatment guide in the management of POMS and most of the data are derived from retrospective studies, case series, and rare randomized controlled trials (RCTs). A large number of new agents approved for the treatment of AOMS in the last two decades by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have not been approved for use in POMS. For POMS, limited safety and efficacy data exist and RCTs studies are needed. Only fingolimod and teriflunomide are approved in Europe for

children.[33–38] Teriflunomide, fingolimod, dimethyl fumarate, rituximab, natalizumab, ocrelizumab, and alemtuzumab are used as primary/secondary or tertiary care in different positions in each country. Individualized treatment should also be considered in the POMS group. In addition to the education level of patients and their families, their preferences, disease activity, and prognostic parameters are among the most important factors in determining the treatment.

In previous studies on treatments used in POMS, both the recurrence risk and new radiological activity were found to be higher in injectable DMDs (iDMDs) than in newer DMDs (nDMDs). Indeed, Krysko et al. found lesion burden and contrast-enhancing lesions to be lower in the nDMD group.[39] However, in the study of Solmaz et al., an increase in disease activity was observed in both the iDMD and nDMD groups at the end of 2 years. Abdel-Mannan et al., on the other hand, compared two treatment groups for attack frequency and found that the frequency of attacks remained constant in the nDMD group compared to the iDMD group.[40] A study which followed large numbers of POMS cases for nearly 20 years showed that the time to reach different milestone EDSS points had decreased significantly in recent years. This can be attributed to early initiation of highly effective drugs in the pediatric age.[41]

Apart from classifying treatment options as injectable and newer, there is another classification based on effectiveness, which has been discussed in recent years and tried to reach a consensus. According to the 2015 British Association of Neurologists guidelines, DMDs are considered in two broad classes. Accordingly, drugs that reduce attacks by more than 50% are regarded as high-effective treatments, and those that reduce attacks by 30%–50% as intermediate-effective treatments.[42] While prevention of attacks is considered in this classification based on RCTs, there is another approach that focuses on ARR. RR $\leqslant$ 0.5 corresponds to high efficacy, while RR $>$ 0.5 and $\leqslant$ 0.7 correspond to moderate efficacy. Samjoo et al. reviewed newly emerging DMDs in terms of efficacy in 2021. In all, 18 DMDs were evaluated in this study and, based on previous approaches (efficacy on relapse prevention), the high efficacy class included alemtuzumab, cladribine, natalizumab, and ofatumumab, while the intermediate efficacy class included dimethyl fumarate, fingolimod, glatiramer acetate, interferon-beta (IFN-β) preparations, ocrelizumab, ozanimod (both doses), and teriflunomide. For the second classification approach (approach based on ARR), the probability of fingolimod to be highly effective treatments is $\geqslant$50% compared to 99% for alemtuzumab, natalizumab, ocrelizumab, and ofatumumab. In the light of all this information, the treatment and management of POMS are accompanied by many difficulties including safety issues of more concern than in the adult group, particularly because of the expected longer duration of treatment. Both the high disease activity in the POMS group and the positive effect of early treatment on long-term outcomes in this group have drawn attention to the use of fingolimod in the POMS group in recent years. Fingolimod has been shown to be effective in many studies and has been used safely in the AOMS group for many years. This makes it easier to use in the POMS group with high disease activity. In this review, the efficacy and safety data for the use of fingolimod in the POMS group are discussed with current RCTs and case reports.[17,18,43] Studies of fingolimod, siponimod, and ofatumumab in still ongoing pediatric MS may also provide important data on both safety and efficacy (NCT04926818). The treatment management of the POMS group seems to evolve toward both early and effective treatments.

Fingolimod in pediatric-onset multiple sclerosis

PARADIGMS trial

The PARADIGMS trial, the first randomized controlled trial completed in pediatric patients, was conducted between June 2013 and August 2016 under the supervision of the FDA and EMA, and a total of 80 centers from 25 countries participated.[44] Among the patients aged 10–17 who were diagnosed according to the IPMSSG criteria, those who had one attack in the last year or two attacks in the last 2 years or at least one enhancing lesion in the last 6 months were included in the study. The study was carried out for 2 years as two parallel-group, double-blind, randomized trial including active drug and IFN-β-1a treatments. One of the most important limitations of the study was the exclusion of patients under 10 years of age. Therefore, its use in daily clinical practice was restricted and led to the approval only in the older age group.

Real-world data

The first retrospective study in childhood was published by Fragoso et al. in 2015 and included 17 patients with a follow-up period of 8.6 months (range: 1–18 months).[45] The second study was performed by Huppke et al. in Germany and examined 27 POMS patients. In this study, clinical and radiological findings of 23 patients were compared before and after fingolimod treatment.[46]

One of the largest cohorts investigating POMS and disease-modifying therapies detected 37 patients using fingolimod accounting for 5% of the whole cohort and 14% of users of nDMDs.[10] A recent study from Turkey found higher rates: 13% of the patients were under fingolimod treatment, amounting to 38% of the nDMD users.[47] Unfortunately, data are limited as these studies did not emphasize drug efficacy and safety (Table 1).

Besides these studies, there are some case series and reports in the literature about fingolimod treatment. These are limited by non-uniform presentation of clinical/radiological findings and side effects, and variable follow-up of patients.

Table 1. Real-world data studies on pediatric MS and fingolimod.

Effectivity data for fingolimod in POMS	Number of the patients	Treatment duration (months)	ARR before fingolimod	ARR after fingolimod	EDSS progression	Number of patient with attack
Fragoso et al.[45]	17	8.6	2.8	0.05	8 stable 9 improved	1
Huppke et al.[46a]	16	11.6	1.69	0.42	NA	NA
Gontika et al.[48]	7	36	1.8	0.74	0	4
Zanetta et al.[49]	2	24	NA	NA	0	0
Borriello et al.[50]	2	44	1.5	0	0	0
Capobianco et al.[51]	1	24	1	0	0	0
Petruzzo et al.[52]	1	NA	NA	NA	NA	NA
Ferilli et al.[53]	3	14	NA	0	0	0
Immovili et al.[54]	1	24	2	0	0	0
Amidei et al.[55]	1	24	2	0	0	0

NA: not applicable.
[a]Sixteen patients only pretreated with a first-line DMD are shown.

Effectiveness of fingolimod

Concerning the PARADIGMS study, 8 (7.5%) of 107 patients who received fingolimod and 26 (24.4%) of 108 patients who received IFN-β-1a discontinued before the end of the study. While no early discontinuation due to inefficacy was observed in the fingolimod group, 13 patients in the IFN-β-1a group were withdrawn from the study for this reason.

Effect of fingolimod on relapse rate. As the primary endpoint, the number of attacks per year after 2 years was 0.12 in the fingolimod group and 0.67 in the interferon group at PARADIGMS. The rate of patients who did not have an attack was 85.7% in the fingolimod group and 38.8% in the interferon group.

According to the results of Fragoso, patients had an average of 2.8 attacks per year before fingolimod, while only one patient developed an attack after treatment.[45] Huppke et al. demonstrated a 75% decrease in the attack rate. Examination of case reports and series showed attacks in 4 of 17 patients.[46,48–55]

Effect of fingolimod on disability progression. Disability assessment was best performed in the PARADIGMS study. The mean baseline EDSS scores were 1.5 in the fingolimod group and 1.6 in the IFN β-1a group. The proportion of patients whose EDSS increased for 3 months was found to be 77.2% less in the fingolimod group than those receiving interferon.

Fragoso et al. demonstrated that eight patients had maintained their initial EDSS level while nine patients have improved.[45] Similarly, none of the patients had worse EDSS score after fingolimod in case reports.[48–55]

Effects of fingolimod on magnetic resonance imaging lesion load. Recently, the effect of fingolimod versus IFN β-1a on magnetic resonance imaging (MRI) outcomes and post hoc analyses of MRI data from the PARADIGMS study was published.[56] The number of new or enlarged T2 lesions was 4.39 in the fingolimod group compared to 9.27 in the interferon group. Regarding enhancing lesions, there were 0.44 in the fingolimod group and 1.28 in the interferon group per imaging ($p < 0.001$). Similarly, the proportion of patients free of new/enlarging T2 lesions was higher in fingolimod-treated patients compared with those treated with IFN β-1a (16.0% versus 3.9%, $p = 0.011$).[57]

Fragoso et al. demonstrated that a new T2 lesion was found in only one of 12 patients who underwent follow-up imaging.[45] Huppke et al. found an 81% decrease in the number of new T2 lesions, and a 93% decrease in the number of enhancing lesions, demonstrating the superiority of fingolimod treatment over conventional treatments.[46]

Effect of fingolimod on brain atrophy. The loss of brain volume was evaluated only in PARADIGMS and this rate was −48% in the fingolimod group and −80% in the interferon group, and significantly less atrophy development was observed at the treatment arm.

Effect of fingolimod on health-related quality of life. The Pediatric Quality of Life scale and its Emotional, Social and School Functioning subscales were performed in all study participants at PARADIGMS showing a significant effect on all of the Pediatric Quality of Life scale and subscale scores, except for Social Functioning.[56]

Safety of fingolimod

When the PARADIGMS study was evaluated in terms of the side effect profile, the total number of side effects was slightly higher in the interferon group (fingolimod 88.8% versus interferon 95.3%). However, the number of patients

Table 2. Fingolimod-related side effects and related studies.

Safety data for fingolimod in POMS	Side effects in studies
PARADGIMS study[44]	Seizures in six patients Leukopenia in two patients Macular edema, agranulocytosis, arthralgia, bladder spasm, dyspepsia, autoimmune uveitis, alanine transaminase and gamma-glutamyl transpeptidase elevation, second-degree AV block, dysuria, gastrointestinal system necrosis (intussusception or colon necrosis), hypersensitivity vasculitis, weakness, rectal tenesmus, and small intestine obstruction in one patient
Cardiovascular system	Second-degree heart block has been reported in a case[52]
Macular edema	One patient[44]
Liver enzymes	Asymptomatic elevation[48]
Lymphocyte count and infections	No increased risk of infection[46] Cough, urinary tract infection[44]
PML	No reported cases[58]

PML: progressive multifocal leukoencephalopathy.

requiring treatment interruption due to side effects was 12 in the fingolimod group, compared to 3 for interferon. Three patients in the fingolimod group and two patients in the interferon group were permanently withdrawn from the study due to side effects. Also, serious side effects were more common in the fingolimod group (fingolimod 16.8% versus interferon 6.5%). Some of these side effects were seizures in six patients, leukopenia in two patients, macular edema, agranulocytosis, arthralgia, bladder spasm, dyspepsia, autoimmune uveitis, alanine transaminase and gamma-glutamyl transpeptidase elevation, second-degree atrioventricular (AV) block, dysuria, gastrointestinal system necrosis (intussusception or colon necrosis), hypersensitivity vasculitis, weakness, rectal tenesmus, and small intestine obstruction in one patient (Table 2).

The proportion of children who had epileptic seizures in PARADIGMS was substantially higher than what was known in adults' clinical trials such as FREEDOMS and TRANSFORMS studies. This is probably due to the general characteristics of the pediatric population since children are more prone to seizures. However, this should be kept in mind when starting fingolimod in the pediatric group.

Effects on the cardiovascular system. Sphingosine 1 phosphate receptors are expressed in myocytes, sinus node, and AV node cells. With the stimulation of these receptors, potassium ions pass into the cell and slow the heart rate and conduction rate. Therefore, transient and mostly asymptomatic bradycardia, and even slowing of AV conduction (though less frequently) can be observed in most patients at the first dose of fingolimod therapy. The first dose must be administered in a hospital setting to monitor bradycardia and detect AV block. Second-degree heart block has been reported in a case in childhood.[52]

Effects on the retina. Sphingosine 1 phosphate receptors expressed in vascular endothelial cells play an important role in regulating vascular permeability and protecting endothelial barrier integrity. One of the side effects that occur due to the deterioration of this balance is macular edema. In FREEDOMS and TRANSFORMS studies, which concern adult patients, macular edema was detected in 0.7%. When studies involving childhood are evaluated, macular edema was detected in only one patient in the PARADIGMS study (28/10,000).

Effects on the liver enzymes. Also in FREEDOMS, liver function tests increased three times in 8% of the patients and five times in 1.8% but returned to normal within 2 months after the treatment was interrupted. Similarly, a low rate of asymptomatic alanine transaminase increases was found in pediatric studies.[41,48] Only one retrospective study pointed out a patient that had to stop medication due to liver enzyme elevation.[58]

Lymphocyte count and effects on infection. The mechanism of action is to keep lymphocytes in lymph nodes, but lymphopenia occurs as side effect. If the lymphocyte levels decrease below 200 cells/μL in the follow-up of the patients, temporary interruption of the treatment should be considered. In general, lymphocyte levels return to normal after about 2 months. However, the waiting time after drug withdrawal should be carefully monitored for disease reactivation or rebound due to drug withdrawal and this period should be kept as short as possible. Studies with a larger population of adult patients have shown that the decrease in lymphocyte count does not significantly increase the risk of infection.

Recently, temporal profile of lymphocyte counts and relationship with infections were published covering 4 years of PARADIGMS extension study. Study group absolute lymphocyte count rapidly reduced to 29.9%–34.4% of baseline values within 2 weeks of fingolimod treatment and stabilized at this level. Only three patients had levels below 0.2×10^9/L and opportunistic infections were not observed nor was there an increase in the infection risk.[59]

Hamdy et al. reported a patient who stopped fingolimod due to blood count abnormality.[58] In the study conducted by Huppke et al., three patients had transient lymphopenia, one patient had transient cough, and one patient had urinary tract infection.[46]

PML risk. PML is a rare opportunistic infection seen as a result of JCV activation. It has become an important side effect with the use of more effective drugs in the treatment of MS. Its rate in the general population is 0.2/100,000 people. When Berger et al. evaluated fingolimod data up to August 2017, they found that fingolimod was used in approximately 217,000 patients, corresponding to a total of 480,000 patient-years. Based on these data, the current risk of PML was found to be 0.069/1000 patients.[60] However, no PML due to fingolimod use in childhood was detected so far.

Malignancy. Basal cell carcinoma cases have been reported in patients treated with fingolimod in AOMS. In both the FREEDOMS study and the FREEDOMS II study, it was reported that more basal cell carcinoma developed in patients receiving fingolimod than placebo. It is essential to be alert to skin lesions and a medical evaluation of the skin should be performed at the start of treatment, and then at least annually. No cancers were reported in PARADIGMS or other studies performed on children. The JCV seroprevalence was 60% seropositivity in the adult population, compared to 33.3% in the pediatric group, and seroconversion increases with age. This may result in a lower risk of drug-induced PML in pediatric patients compared to adult patients.[61–63]

Limitations

The main goal in this review is to show the effectiveness of fingolimod, which has been used in AOMS for many years, with real-life data, and not to pose a serious adverse event in terms of security. In fact, before a treatment option can be used in the POMS group, it is necessary to gain experience and data accumulation in adults. Based on this fact, in this review, we summarize both the phase studies and post-marketing studies of fingolimod, which is the first oral agent approved in POMS, and to draw more attention to the use of fingolimod in the POMS group. However, in this review, data on the treatment of POMS group younger than 10 years of age (missing data), which can progress aggressively, could not be given. The most important limitation of this review is the inability to include all articles on pediatric MS and its treatment. Because the designs of the studies were based on different parameters, it was not possible to analyze the common data obtained from the studies. In addition, case reports based on individual experiences are not included as they may shift the focus of the article. This is actually a limitation that is always encountered as a general problem. In addition, the lack of long-term studies of fingolimod in POMS may warrant a later update of this review.

Conclusion

When many adult MS studies and limited POMS studies are evaluated together, fingolimod appears to significantly reduce the annual attack rate and has positive effects on MRI lesion activity and brain atrophy compared to injectable treatments. Long-term studies and real-life data from larger numbers of patients are needed to support initial encouraging safety and efficacy data in the POMS group. Although the importance of starting effective treatments in the early period is known even in AOMS, treatment management in POMS cannot be performed at the same pace. Reasons for this include the lack of long-term safety data for children and issues with health insurance coverage, which may hinder accelerated access to effective treatments. Therefore, it may be important to periodically review and draw attention to all data.

Acknowledgements

The authors thank the patients for their participation and all investigators and staff associated with this study.

Author contributions

SO and BA have involved in concept, design, supervision, and critical reviews. BPC and BK have involved in resource, materials, data collection and/or processing, and writing. BK, BPC, and CO have involved in literature search. Thanks to CO (Novartis Pharma AG) for the support in the literature and evidence research.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical issue

This study does not require ethical approval or patient consent, as it is a review of publications for the pediatric use of fingolimod.

Disclosure statement

SO received honoraria for lectures and advisory boards from Sanofi Genzyme, Roche, Merck Serono, Novartis, and Teva. Also he received national/international congress support from Sanofi Genzyme, Roche, Merck Serono, Novartis, and Teva. BPC received honoraria for lectures advisory boards from Sanofi Genzyme, Merck Serono, Novartis, and Teva. Also he received national/international congress support from Sanofi Genzyme, Roche, Merck Serono, Novartis, and Teva. BA received honoraria for advisory boards from Novartis. BK received honoraria for advisory boards from Novartis.

ORCID iD

Bilge Piri Cinar https://orcid.org/0000-0002-4884-0717

References

1. Belman AL, Krupp LB, Olsen CS, et al. Characteristics of children and adolescents with multiple sclerosis. *Pediatrics* 2016; 138(1): e20160120.
2. Renoux C, Vukusic S, Mikaeloff Y, et al. Natural history of multiple sclerosis with childhood onset. *N Engl J Med* 2007; 356(25): 2603–2613.
3. Duquette P, Murray TJ, Pleines J, et al. Multiple sclerosis in childhood: clinical profile in 125 patients. *J Pediatr* 1987; 111(3): 359–363.
4. Fragoso YD, Ferreira ML, Morales Nde M, et al. Multiple sclerosis starting before the age of 18 years: the Brazilian experience. *Arq Neuropsiquiatr* 2013; 71(10): 783–787.
5. Ghezzi A, Deplano V, Faroni J, et al. Multiple sclerosis in childhood: clinical features of 149 cases. *Mult Scler* 1997; 3(1): 43–46.
6. Reinhardt K, Weiss S, Rosenbauer J, et al. Multiple sclerosis in children and adolescents: incidence and clinical picture – new insights from the nationwide German surveillance (2009-2011). *Eur J Neurol* 2014; 21(4): 654–659.
7. Wilbur C and Yeh EA. Improving outcomes in pediatric multiple sclerosis: current and emerging treatments. *Paediatr Drugs* 2019; 21(3): 137–152.
8. McKay KA, Hillert J and Manouchehrinia A. Long-term disability progression of pediatric-onset multiple sclerosis. *Neurology* 2019; 92(24): e2764–e2773.
9. Yılmaz Ü, Anlar B and Gücüyener K; Turkish Pediatric Multiple Sclerosis Study Group. Characteristics of pediatric multiple sclerosis: the Turkish pediatric multiple sclerosis database. *Eur J Paediatr Neurol* 2017; 21(6): 864–872.
10. Iaffaldano P, Simone M, Lucisano G, et al. Prognostic indicators in pediatric clinically isolated syndrome. *Ann Neurol* 2017; 81(5): 729–739.
11. Solmaz İ and Öncel İ. Evolution of clinically isolated syndrome to pediatric-onset multiple sclerosis and a review of the literature. *Turk J Med Sci* 2022; 52(4): 1281–1287.
12. Çinar BP and Özakbaş S. Prediction of conversion from clinically isolated syndrome to multiple sclerosis according to baseline characteristics: a prospective study. *Noro Psikiyatr Ars* 2018; 55(1): 15–21.
13. Kolčava J, Kočica J, Hulová M, et al. Conversion of clinically isolated syndrome to multiple sclerosis: a prospective study. *Mult Scler Relat Disord* 2020; 44: 102262.
14. de Chalus A, Taveira M and Deiva K. Pediatric onset multiple sclerosis: future challenge for early diagnosis and treatment. *Presse Med* 2021; 50(2): 104069.
15. Benson LA, Healy BC, Gorman MP, et al. Elevated relapse rates in pediatric compared to adult MS persist for at least 6 years. *Mult Scler Relat Disord* 2014; 3(2): 186–193.
16. Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. *Mult Scler* 2013; 19(10): 1261–1267.
17. Harding KE, Liang K, Cossburn MD, et al. Long-term outcome of paediatric-onset multiple sclerosis: a population-based study. *J Neurol Neurosurg Psychiatry* 2013; 84(2): 141–147.
18. Hamdy SM, Abdel-Naseer M, Shalaby NM, et al. Pediatric-onset multiple sclerosis in Egypt: a multi-center registry of 186 patients. *Neuropsychiatr Dis Treat* 2018; 14: 631–640.
19. Renoux C, Vukusic S and Confavreux C. The natural history of multiple sclerosis with childhood onset. *Clin Neurol Neurosurg* 2008; 110(9): 897–904.
20. Hacohen Y, Mankad K, Chong WK, et al. Diagnostic algorithm for relapsing acquired demyelinating syndromes in children. *Neurology* 2017; 89(3): 269–278.
21. Duignan S, Wright S, Rossor T, et al. Myelin oligodendrocyte glycoprotein and aquaporin-4 antibodies are highly specific in children with acquired demyelinating syndromes. *Dev Med Child Neurol* 2018; 60(9): 958–962.
22. Duignan S, Brownlee W, Wassmer E, et al. Paediatric multiple sclerosis: a new era in diagnosis and treatment. *Dev Med Child Neurol* 2019; 61(9): 1039–1049.
23. Öztürk Z, Gücüyener K, Soysal Ş, et al. Cognitive functions in pediatric multiple sclerosis: 2-years follow-up. *Neurol Res* 2020; 42(2): 159–163.
24. Amato MP, Ponziani G, Pracucci G, et al. Cognitive impairment in early-onset multiple sclerosis. Pattern, predictors, and impact on everyday life in a 4-year follow-up. *Arch Neurol* 1995; 52(2): 168–172.
25. Amato MP, Goretti B, Ghezzi A, et al. Cognitive and psychosocial features of childhood and juvenile MS. *Neurology* 2008; 70(20): 1891–1897.
26. Gogtay N, Giedd JN, Lusk L, et al. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci U S A* 2004; 101(21): 8174–8179.
27. Sowell ER, Thompson PM, Tessner KD, et al. Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: inverse relationships during postadolescent brain maturation. *J Neurosci* 2001; 21(22): 8819–8829.
28. Wierenga LM, Langen M, Oranje B, et al. Unique developmental trajectories of cortical thickness and surface area. *Neuroimage* 2014; 87: 120–126.
29. Kerbrat A, Aubert-Broche B, Fonov V, et al. Reduced head and brain size for age and disproportionately smaller thalami in child-onset MS. *Neurology* 2012; 78(3): 194–201.
30. Aubert-Broche B, Weier K, Longoni G, et al. Monophasic demyelination reduces brain growth in children. *Neurology* 2017; 88(18): 1744–1750.
31. Ghezzi A, Amato MP, Edan G, et al. The introduction of new medications in pediatric multiple sclerosis: open issues and challenges. *Mult Scler* 2021; 27(3): 479–482.
32. Erdal JL, Kopp TI, Blinkenberg M, et al. Clinical characteristics and use of disease modifying therapy in the nationwide Danish cohort of paediatric onset multiple sclerosis. *Mult Scler Relat Disord* 2020; 37: 101431.
33. Konuskan B and Anlar B. Treatment in childhood central nervous system demyelinating disorders. *Dev Med Child Neurol* 2019; 61(11): 1281–1288.
34. https://www.fda.gov/news-events/press-announcements/fda-expands-approval-gilenya-treat-multiple-sclerosis-pediatric-patients
35. Macaron G, Feng J, Moodley M, et al. Newer treatment approaches in pediatric-onset multiple sclerosis. *Curr Treat Options Neurol* 2019; 21(10): 50.

36. Paik J. Teriflunomide: pediatric first approval. *Paediatr Drugs* 2021; 23(6): 609–613.
37. Solmaz I, Acar Ozen P, Parlak S, et al. Newer disease modifying treatments in pediatric onset multiple sclerosis: experience from a single center. *Eur J Paediatr Neurol* 2022; 39: 110–115.
38. Jakimovski D, Awan S, Eckert SP, et al. Multiple sclerosis in children: differential diagnosis, prognosis, and disease-modifying treatment. *CNS Drugs* 2022; 36(1): 45–59.
39. Abdel-Mannan OA, Manchoon C, Rossor T, et al. Use of disease-modifying therapies in pediatric relapsing-remitting multiple sclerosis in the United Kingdom. *Neurol Neuroimmunol Neuroinflamm* 2021; 8(4): e1008.
40. Krysko KM, Graves JS, Rensel M, et al. Real-world effectiveness of initial disease-modifying therapies in pediatric multiple sclerosis. *Ann Neurol* 2020; 88(1): 42–55.
41. Baroncini D, Simone M, Iaffaldano P, et al. Risk of persistent disability in patients with pediatric-onset multiple sclerosis. *JAMA Neurol* 2021; 78(6): 726–735.
42. Scolding N, Barnes D, Cader S, et al. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. *Pract Neurol* 2015; 15(4): 273–279.
43. Samjoo IA, Worthington E, Drudge C, et al. Efficacy classification of modern therapies in multiple sclerosis. *J Comp Eff Res* 2021; 10(6): 495–507.
44. Chitnis T, Arnold DL, Banwell B, et al. Trial of Fingolimod versus Interferon Beta-1a in pediatric multiple sclerosis. *N Engl J Med* 2018; 379(11): 1017–1027.
45. Fragoso YD, Alves-Leon SV, Barreira AA, et al. Fingolimod prescribed for the treatment of multiple sclerosis in patients younger than age 18 years. *Pediatr Neurol* 2015; 53(2): 166–168.
46. Huppke P, Huppke B, Ellenberger D, et al. Therapy of highly active pediatric multiple sclerosis. *Mult Scler* 2019; 25(1): 72–80.
47. Krysko KM, Graves J, Rensel M, et al. Use of newer disease-modifying therapies in pediatric multiple sclerosis in the US. *Neurology* 2018; 91(19): e1778–e1787.
48. Gontika M, Skarlis C, Markoglou N, et al. Fingolimod as a first- or second-line treatment in a mini-series of young Hellenic patients with adolescent-onset multiple sclerosis: focus on immunological data. *Neurol Sci* 2022; 43(4): 2641–2649.
49. Zanetta C, Filippi M and Moiola L. Fingolimod as an effective therapeutic strategy for pediatric relapsing-remitting multiple sclerosis: two case reports. *Neurol Sci* 2021; 42(Suppl 1): 9–13.
50. Borriello G and Pozzilli C. Long-term fingolimod treatment in two pediatric patients with multiple sclerosis. *Neurol Sci* 2021; 42(Suppl 1): 29–36.
51. Capobianco M, Bertolotto A and Malucchi S. Fingolimod as first-line treatment in pediatric-onset multiple sclerosis: a case report. *Neurol Sci* 2021; 42(Suppl 1): 25–28.
52. Petruzzo M and Lanzillo R. Asymptomatic bradycardia after first fingolimod dose in a pediatric patient with multiple sclerosis – a case report. *Neurol Sci* 2021; 42(Suppl 1): 37–39.
53. Ferilli MAN, Papetti L and Valeriani M. Fingolimod in pediatric multiple sclerosis: three case reports. *Neurol Sci* 2021; 42(Suppl 1): 19–23.
54. Immovilli P, Rota E, Morelli N, et al. Two-year follow-up during fingolimod treatment in a pediatric multiple sclerosis patient still active on first-line treatment. *Neurol Sci* 2021; 42(Suppl 1): 15–18.
55. Amidei A, Siciliano G and Pasquali L. Efficacy of fingolimod after switching from interferon β-1a in an adolescent with multiple sclerosis: case report. *Neurol Sci* 2021; 42(Suppl 1): 5–7.
56. Krupp L, Banwell B, Chitnis T, et al. Effect of fingolimod on health-related quality of life in paediatric patients with multiple sclerosis: results from the phase 3 PARADIG*MS* Study. *BMJ Neurol Open* 2022; 4(1): e000215.
57. Arnold DL, Banwell B, Bar-Or A, et al. Effect of fingolimod on MRI outcomes in patients with paediatric-onset multiple sclerosis: results from the phase 3 PARADIG*MS* study. *J Neurol Neurosurg Psychiatry* 2020; 91(5): 483–492.
58. Hamdy SM, Abdel-Naseer M, Shalaby NM, et al. Pediatric-onset multiple sclerosis in Egypt: a multi-center registry of 186 patients. *Neuropsychiatr Dis Treat* 2018; 14: 631–640.
59. Chitnis T, Arnold DL, Banwell B, et al. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. *N Engl J Med* 2018; 379(11): 1017–1027.
60. Berger JR, Cree BA, Greenberg B, et al. Progressive multifocal leukoencephalopathy after fingolimod treatment. *Neurology* 2018; 90(20): e1815–e1821.
61. Hennes EM, Kornek B, Huppke P, et al. Age-dependent seroprevalence of JCV antibody in children. *Neuropediatrics* 2016; 47(2): 112–114.
62. Lundstig A and Dillner J. Serological diagnosis of human polyomavirus infection. *Adv Exp Med Biol* 2006; 577: 96–101.
63. Zhong S, Zheng HY, Suzuki M, et al. Age-related urinary excretion of BK polyomavirus by nonimmunocompromised individuals. *J Clin Microbiol* 2007; 45(1): 193–198.