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Multiple Sclerosis Therapies in Pediatric Patients: Challenges and Opportunities

JASNA JANČIĆ¹ • BLAŽO NIKOLIĆ¹ • NIKOLA IVANČEVIĆ¹ • BORIS HENČIĆ² • JANKO SAMARDŽIĆ²

¹Clinic of Neurology and Psychiatry for Children and Youth, Medical Faculty, University of Belgrade, Belgrade, Serbia; ²Institute of Pharmacology, Clinical Pharmacology and Toxicology, Medical Faculty, University of Belgrade, Belgrade, Serbia

Author for correspondence: Janko Samardžić, Institute of Pharmacology, Clinical Pharmacology and Toxicology, Medical Faculty, University of Belgrade, Serbia. E-mail: jankomedico@yahoo.es

Doi: <http://dx.doi.org/10.15586/codon.multiplesclerosis.2017.ch3>

Abstract: Multiple sclerosis (MS) is an autoimmune, chronic, inflammatory, and demyelinating disease of the central nervous system (CNS). The etiology of MS is most likely multifactorial; it is dependent on genetic, autoimmune, and environmental factors, with a variable course among patients. The two main clinical events that characterize MS are relapses and progression. In recent years, diagnosis and treatment of pediatric MS has drawn attention of the scientific community. Management of pediatric MS focuses on reducing relapses and symptoms via administration of disease-modifying drugs (DMDs) and specific symptomatic treatment. A multidisciplinary approach to pediatric MS treatment is preferred, which aims at alleviating and preventing the accumulation of neurological deficits. MS therapy should be based on DMDs, that is, immunomodulatory drugs. These drugs, which sequester immune system activity, are further subdivided into two categories: first-line and second-line immunomodulatory therapy. First-line immunomodulatory therapy (interferon beta-1a, interferon beta-1b,

In: *Multiple Sclerosis: Perspectives in Treatment and Pathogenesis*. Ian S. Zagon and Patricia J. McLaughlin (Editors), Codon Publications, Brisbane, Australia. ISBN: 978-0-9944381-3-3; Doi: <http://dx.doi.org/10.15586/codon.multiplesclerosis.2017>

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and glatiramer acetate) is ineffective (either no response or partial response) in roughly 30% of patients. Patients with a poor response to first-line therapy require second-line immunomodulatory therapy (natalizumab, mitoxantrone, fingolimod, teriflunomide, azathioprine, rituximab, dimethyl fumarate, daclizumab, alemtuzumab, and ocrelizumab). In addition to immunomodulatory drugs, treatment of relapses also involves the use of high intravenous doses of corticosteroids, administration of intravenous immunoglobulins, and plasmapheresis.

Key words: Etiology; Immunomodulatory therapy; Multiple sclerosis; Pediatrics; Therapy

Introduction

Multiple sclerosis (MS) is an autoimmune, chronic, inflammatory, and demyelinating disease of the central nervous system (CNS) (1). The onset of MS occurs predominantly between the second and the fourth decade of life, but diagnosis in those older than 50, as well as in children, albeit less frequent, has also been observed. In the 19th century, Prof. Jean-Martin Charcot provided the first pathological and clinical description of MS, labeling it *sclerose en plaques* (2). The subsequent decades witnessed extensive etiological, pathophysiological, and pharmacological studies regarding MS, from the discovery of its genetic basis to the implementation of immunomodulatory therapy (3–5). In recent years, diagnosis and treatment of pediatric MS has drawn attention of the scientific community (6). The clinical characteristics, laboratory analyses, and neuroimaging techniques may significantly differ in children versus adults (7), whereas an individual approach remains crucial for the early diagnosis, as well as for the treatment of pediatric MS.

Although the exact etiology is still unknown, MS is most likely a multifactorial disease; it is dependent on genetic, autoimmune, and environmental factors (8). More than 200 genes may play a role in the occurrence of MS, with changes in the human leukocyte antigen (HLA) DRB 1 gene most likely playing the most significant role in initiation (9, 10). Besides genetic factors, the etiopathogenesis of MS may be also associated with an altered immunological response during the Epstein–Barr virus infection, decreased vitamin D levels, and smoking (11–13). Although, some authors reported a link between childhood obesity and MS, this correlation has not been fully clarified; however, the authors believe that this is due to the low levels of vitamin D, since most of the vitamin D is deposited in the adipose tissue (14). Childhood obesity can also increase the risk of MS, independently of vitamin D levels. Low levels of serum vitamin D in mothers, during early stages of pregnancy, can also lead to an increased risk of MS in progeny (14). The consequential production of proinflammatory cytokines during the altered immunological response damages oligodendrocytes and myelin, causing plaques of inflammatory demyelination (15). Moreover, some studies have shown that pediatric patients with MS have 50% higher extent of acute axonal damage compared with adult patients (16). Epidemiological studies show that almost 50% of patients with pediatric and adult MS are from Europe (17). Studies have shown that there are areas with

higher prevalence of MS in the world, such as North America and certain countries in northern Europe (17, 18). The Orkney Islands represent an area that has the highest prevalence of MS, with 300 patients per 100,000 citizens (19), but some studies have also pointed out that Sardinia has the highest prevalence of pediatric MS (20). If we look at the American continent, the rise of African Americans with pediatric MS is noticeable, but still MS is most commonly seen in non-Hispanic white individuals (21).

Clinical Characteristics: Children versus Adults

Although with a variable course among patients, there are two main clinical features that characterize all forms of MS: progression and relapse (22). Progression is characterized by a 6-month period of continuous deterioration in neurological status, while relapse is defined as the occurrence or aggravation of neurological symptoms lasting for more than 24 h (23, 24). These attacks should be separated by at least 30 days in order to be considered a relapse. Normal neurological status is often present during the days between attacks, with some sequelae possible. Pediatric MS is usually diagnosed around 15 years of age (25). The sex ratio varies depending on age (male to female ratio 4:5 at early onset; up to 1:2 after the age of 10), which could indicate the role of sex hormones in its pathogenesis (7, 26). Finally, 6–20% of pediatric patients possess a positive family history for MS (3).

The first attack of neurological symptoms, known as clinically isolated syndrome (CIS), lasts longer than 24 h and is characterized as inflammatory demyelination without encephalopathy (27). According to literature, there is a 30–75% chance of a CIS progressing to MS (28, 29). For the pediatric population, acquired demyelinating syndromes were first classified in 2007 (30), and later updated in 2013 (23). Similar to CIS, radiological isolated syndrome (RIS) has been described in recent years. RIS represents the MRI findings associated with demyelinating diseases. However, a strong correlation between RIS and the development of MS lacks, with approximately 20% of patients with RIS developing MS within the next 5 years (31). Over time, MS eventually leads to significant brain atrophy and thereby loss of brain volume. Global and regional brain atrophy develops gradually in the adult population (32). This is in contrast to pediatric MS, where regional brain atrophy is dominant (33), causing significant cognitive and physical disabilities (34).

The relapsing–remittent (RR) form is most common among children (more than 85% of all patients) (6, 35). Patients with RR MS have no increased risk of advancement to the secondary progressive form despite the growth of the degree of disability (36). Recurrence rates in the pediatric population are higher in the first 3 years than in adults (6). However, the recovery period following a relapse is much shorter in children (1). Long-term disability is slower in pediatric population, but these patients will be more disabled compared to adult-onset MS at a younger age, because of the earlier onset of the disease (37). Furthermore, up-to-date diagnostic techniques have allowed for a much earlier detection of the disease (38). Differential diagnosis should be performed in order to rule out other possible causes with similar clinical signs and symptoms (1, 39, 40).

The revised McDonald's diagnostic criteria are a universally approved scheme for MS diagnosis. Consensus regarding diagnostic criteria for pediatric MS and

related disorders was published in 2007 (30) and most recently updated in 2013 (23). According to Krupp et al., the following criteria should be met prior to the diagnosis of pediatric MS (23, 41). Finally, MRI represents a highly sensitive method for judging disease activity in both adults and children. Children tend to show multiple lesions surrounding the cerebellum and brainstem, in comparison with adults (42). MRI findings with more pronounced lesions are often correlated with increased severity of disability (26).

Treatment of Pediatric MS

Similar to adult therapy, pediatric MS focuses on reducing relapses and symptoms via disease-modifying and symptomatic treatment. Children, however, differ from adults in many physiological and developmental issues, resulting in significant discrepancy for drug efficacy and safety, as well as treatment response. The altered immunomodulatory treatment response in MS may be significantly affected by higher level of CNS inflammation and the differences in neurological damage intensity, restorative capacity, and plasticity (43), as well as by the different immunopathobiological mechanism in children versus adults (6).

IMMUNOMODULATORY THERAPY

MS therapy should be based on disease-modifying drugs (DMDs), that is, immunomodulatory drugs. These drugs are further subdivided into two categories: first-line and second-line immunomodulatory therapy (Figure 1). Current guidelines suggest DMD therapy be also given to pediatric patients, as close to the onset of disease as possible (44). No evident disease activity (NEDA) is the main goal of immunomodulatory therapy, that is, to reduce the number of relapses and disease activity on MRI. At this moment, it is difficult to achieve this in the pediatric population with MS because of the current availability of therapy in the pediatric population (37).

FIRST-LINE IMMUNOMODULATORY THERAPY

Immunomodulatory drugs significantly reduce the frequency and severity of clinical relapses and disease activity, as well as the degree of disability. These drugs, which have been approved by the European Medicines Agency (EMA), are given either intramuscularly (i.m.) or subcutaneously (s.c.) and are generally well tolerated. However, due to their parenteral route of administration, difficulties may arise in pediatric patients (6, 45, 46). Immunomodulatory therapy is a preferred therapy for adults and children older than 12 years of age. Common drugs in this class include interferon beta-1a (Rebif®, Avonex®), interferon beta-1b (Betaferon®), and glatiramer acetate (Copaxone®). Rebif® is given s.c. three times a week in a dose between 22 and 44 µg, whereas Avonex® is given i.m. once a week in a dose of 30 µg. Interferon beta-1b and glatiramer acetate are both given s.c. every other day, at doses of 250 µg and 20 mg, respectively (45). This class of medication reduces relapses in adults by as much as 30% (6, 40). These drugs, with anti-inflammatory and immunomodulatory effects, significantly reduce the

First-line immunomodulatory therapy

- Interferon beta-1a 30 µg i.m. Once a week
- 22–44 µg s.c. Three times a week
- Interferon beta-1b 250 µg s.c. Every other day
- Glatiramer acetate 20 mg s.c. Once a day

Second-line immunomodulatory therapy

- Natalizumab 3–5 mg/kg i.v. Once a month
- Mitoxantrone In a dose of 10–20 mg—up to a total dose of 200 mg i.v. Once every 3 months
- Rituximab 500–1000 mg i.v. Every 6–12 months
- Alemtuzumab 60 mg/week, one year, after the first year 36 mg/week for the following 3 years i.v. Once a day
- Ocrelizumab 600 mg i.v. Every 24 weeks
- Dimethyl fumarate Initial dose 120 mg, therapeutic dose 240 mg p.o. Twice daily
- Fingolimod 0.5 mg p.o. Once a day
- Teriflunomide 7 and 14 mg p.o. Once a day
- Azathioprine 2.5–3 mg/kg p.o. Once a day
- Daclizumab 150 mg s.c. Once a month

Figure 1 First-line and second-line immunomodulatory treatment.

frequency and severity of clinical relapses and disease activity, as shown by MRI of the brain, as well as reduce the degree of disability (39). Results for interferon beta-1a application in young children (aged 2–11 years) versus adolescents (aged 12–17 years) have shown that the safety profile is similar. Younger patients only had increased levels of liver enzymes (47).

Interferons are cytokines crucial for immunoregulation signaling cascades. Their effects range from reduction of lymphocyte cytokines, inhibition of autoreactive T-cells, and induction of anti-inflammatory mediators (6). Interferon beta-1a and beta-1b are DMDs used in MS therapy. Side effects of interferon class medication, based on published findings, include skin reaction at site of injection (more common in s.c. administration than in i.m.), headache, flu-like symptoms, nausea, fatigue, myalgia, anemia, lymphopenia, neutropenia, thyroid dysfunction, allergic reactions (drug eruption, rash, urticaria, and anaphylaxis), epilepsy and convulsive disorder, autoimmune diseases, cartilage and bone disorders, serious infections, and elevated liver enzymes (44, 45). Ibuprofen or paracetamol (acetaminophen) is the therapy of choice for those patients with flu-like symptoms. Monthly liver function tests are necessary during the first 6 months of interferon therapy, followed by once every 3 months until the course is complete. Thyroid function should also be assessed—one to two times per year while on interferon therapy (48).

Glatiramer acetate inhibits effector T-cells and regulates antigen-presenting cells (APCs) and suppressor T-lymphocytes (6). It is a generally well-tolerated immunomodulatory drug and a good option for long-term use (45). In terms of adverse effects of glatiramer acetate use, up-to-date pharmacovigilance studies

are scarce. Available studies suggest that glatiramer acetate may cause a transient flushing-like reaction accompanied by tachycardia (48). Pediatric patients on DMD therapy need to be followed to assess the efficacy and safety of therapy. Their assessment should be performed on MRI every 6–12 months followed by laboratory analyses (blood cell count, kidney function, and liver function) (47).

SECOND-LINE IMMUNOMODULATORY THERAPY

Around 30% of patients are partially responsive or nonresponsive to first-line therapy, requiring second-line immunomodulatory therapy (49). The current recommendation involves switching of these patients to natalizumab or other treatments although these drugs have not been evaluated in children.

Natalizumab (Tysabri®) is a monoclonal antibody that targets $\alpha 4\beta 1$ -integrin, a protein located on most leukocytes, and renders the blood–brain barrier (BBB) impermeable to T-lymphocytes and B-lymphocytes (2). It is given as an intravenous (i.v.) infusion once a month in a dose of 300 mg (50) or 3–5 mg/kg (6). Natalizumab has been shown to reduce the activity of MS and its progression in adult patients. Although currently contraindicated for pediatric use, clinical trials have shown that natalizumab decreases disease activity with fewer side effects in pediatric cases as well (51). Natalizumab reduces relapses by 68% (50) and reduces the number of new T2 lesions on MRI compared to placebo by up to 83% (37). However, it has a high risk of serious side effects, such as progressive multifocal leukoencephalopathy (PML), which can lead to serious disability, hypersensitivity, and infections (6, 49, 51, 52). Prior to beginning natalizumab therapy, it is important to perform JC virus serological testing, as well as secondary testing 3–6 months after in seronegative patients (51). If the patient shows any signs of PML, therapy should be stopped immediately.

Mitoxantrone (Novantrone®) reduces the proliferation of lymphocytes (both T and B). It is administered as a single dose of 10–20 mg (maximal dose of 200 mg) through intravenous infusion once every 3 months (50). Mitoxantrone is generally reserved for patients with severe cases of relapse remitting MS or secondary progressive course of disease (53). This drug should be used with caution as it has high rates of adverse reaction (53). The most common adverse effects of mitoxantrone are cardiotoxicity, risk of cardiomyopathy, leukopenia, nausea, infections, alopecia, fatigue, and amenorrhea (37, 50, 53). There have also been reports of increased risk of colon cancer associated with mitoxantrone (54). Due to the increased risk of cardiotoxicity, it is imperative for patients to undergo frequent echocardiograms, as well as subsequent cardiological tests.

Fingolimod (Gylenia®) tablets (0.5 mg) are taken once daily orally, making it a much easier therapeutic option for patients. The Federal Drug Administration (FDA) approved fingolimod as a first-line therapy for MS, while the EMA has it currently as second line. This drug targets the sphingosine-1-phosphate receptor, preventing the migration of lymphocytes from lymph glands, subsequently reducing the number of lymphocytes in the CNS (6). The efficacy of fingolimod is not only considered to be higher than the other first-line drugs but it is also associated with serious adverse effects, such as abnormal heart rhythm (especially bradycardia) after the first dose of the drug, macular edema, lymphopenia and a rise in hepatic enzymes, malignant tumor proliferation and infections (varicella infections, herpes infections), and PML (37, 55).

Teriflunomide (Aubagio®) tablets (7 and 14 mg) are also administered orally once a day for the treatment of RR forms of MS. Its mechanism of action is the reversible inhibition of dihydroorotate dehydrogenase, thus affecting T-cell and B-cell proliferation (37). This drug is fairly safe, with common side effects such as hepatotoxicity and alopecia (6).

Azathioprine, as an immunosuppressive drug used in adults, antagonizes purine metabolism. Azathioprine is given orally in a dose of 2.5–3 mg/kg/day, and the most common adverse effects include gastrointestinal disturbances, skin rashes, liver toxicity, and cytopenia (50). Cyclophosphamide also represents an immunosuppressive drug with potent cytotoxic effects. In aggressive forms of MS, cyclophosphamide significantly reduced relapse of disease and MRI activity (37, 56). The most common adverse effects include vomiting, transient alopecia, amenorrhea, and osteoporosis, necessitating regular patient follow-ups in order to prevent the development of amenorrhea, sterility, and malignancies, such as bladder cancer and leukemia (6, 37, 50).

Rituximab (Rituxan®) represents a chimeric monoclonal immunoglobulin G1 (IgG1)—kappa antibody that targets the CD20 receptor on activated B-lymphocytes. Rituximab may reduce relapses and MRI activity in MS and Neuromyelitis optica (NMO) in adolescents (37); however, there are only few studies on the use of rituximab in pediatric patients with MS so far (57).

Dimethyl fumarate (Tecfidera®) is administered orally using a dose of 120 mg/240 mg in patients with relapsing forms of MS (58). Although not fully understood, dimethyl fumarate may reduce cytokine production and lymphocyte count, resulting in a decrease in immune cells migratory activity through the BBB (59). Its active metabolite is monomethyl fumarate and the most common adverse effects include itching and redness, nausea and vomiting, abdominal pain and diarrhea, lymphopenia, PML, vision problems, and hypersensitivity reactions (60).

Daclizumab (Zinbrya®) is given s.c. once a month in a dose of 150 mg. It represents a monoclonal humanized antibody that selectively binds to the IL-2 receptor alpha-chain. Daclizumab decreases relapse rate and the incidence of new lesions on MRI (61, 62). The most common adverse effects include serious infections, gastrointestinal disturbances, depression, liver toxicity with an elevation of liver enzymes, and serious cutaneous events. There is only one clinical trial, consisting of seven patients, on daclizumab in children with MS so far (61). It reduced the clinical and MRI disease activity in pediatric patients, while the side effects were mild (61, 62).

Alemtuzumab (Lemtrada®) is administered i.v. with a specific dosage regime. First-time treatment consists of 12 mg/day for the first 5 days (60 mg/week), which is continued for 1 year. After the first year, the patient should receive 12 mg/day for 3 days (36 mg/week) for the following 3 years. Alemtuzumab is a human monoclonal antibody against CD52, which binds to the surface of CD4+ and CD8+ cells, B cells, and monocytes. Its highest efficacy is seen during the active inflammation stage of MS. Alemtuzumab has similar efficacy to natalizumab in patients with RR MS. It is also more efficient in lowering the number of relapses in patients receiving fingolimod and interferon beta (63). For now, a higher risk of infection has been associated with alemtuzumab therapy compared with those receiving interferon beta. The most common adverse effects are infusion reactions (headache, swelling, fever, nausea, urticaria, and fatigue), which are most likely

due to cytokine release after cellular lysis (64). Due to the risk of infusion reactions, it is imperative to monitor patients receiving alemtuzumab infusion therapy very closely, especially 2–3 h post-infusion (64, 65). Furthermore, the same studies have shown idiopathic thrombocytopenia purpura and autoimmune nephropathy as possible adverse effects (64). Thus far, no studies regarding alemtuzumab's efficacy in pediatric MS patients have been published.

Ocrelizumab (Ocrevus®) is a monoclonal antibody with selective affinity for CD20+ B cells. It is given at a dose of 600 mg i.v. every 24 weeks. It is approved by the FDA for use in RR and primary progressive MS patients. This is the first medication that is approved for adults with primary progressive MS. Studies (OPERA I and OPERA II) show that ocrelizumab lowers relapses by an additional 46–47% in comparison with interferon beta-1a therapy (66). Therapy has also shown lowering progressive disability up to 40% as measured by the Expanded Disability Status Scale (EDSS). Furthermore, ocrelizumab also lowers brain atrophy visible via MRI (66). The most common side effects of therapy are infections, infusion reactions, and increased risk of tumor (66, 67).

TREATMENT OF RELAPSES AND SPECIFIC SYMPTOMS

The aim of MS therapy is to alleviate and prevent the accumulation of neurological deficits (68). During a relapse, it is crucial to quickly and efficiently assess the clinical status and begin appropriate therapy (69). High doses (20–30 mg/kg, max 1000 mg/day) of i.v. corticosteroids (methylprednisolone) are recommended once a day, preferably in the morning, alongside gastroprotective medication. Short courses of high-dose corticosteroid treatment reduce side effects of systemic corticosteroid use. Side effects in children include mood disorders, insomnia, hypertension, arrhythmias, facial erythema, higher appetite and body mass, acne, hyperglycemia, and gastric ulcerations (necessitates the use of concomitant gastroprotective agents) (7, 68). Before introduction of corticosteroids, it is necessary to educate the parents and patients about all of the side effects. If even after the completion of i.v. corticosteroid therapy full recovery is not attained, oral prednisone at a dose of 1 mg/kg daily (max dose 60 mg/day) can be initiated (69). If corticosteroid therapy results in little or no improvement in clinical picture, or a deterioration in the patient's condition, a 5-day course of i.v. immunoglobulins at 0.4 g/kg/day can be administered. Another option for patients unresponsive to conventional relapse therapy, or for those patients suffering from rapid progressive disease, is plasmapheresis (1, 69). In severe cases, patients may arrive in a life-threatening condition, wherein primary concern should be the establishment of proper airway and circulatory function (69).

Symptomatic therapy should be directed toward eliminating specific symptoms. The most common symptoms that occur in children are pain, depression, anxiety, fatigue, stiffness, interference with urination, and sexual dysfunction. Adequate and effective symptomatic therapy has a positive effect on the quality of life of pediatric patients with MS. Pain associated with MS should be treated according to the algorithm for neuropathic pain therapy, namely, tricyclic antidepressants, gabapentin doses of 600 mg/day, pregabalin, 5% lidocaine, and tramadol (62, 70). Fatigue is a common symptom in MS, occurring in about 76% of cases (62). Patients who complain of fatigue should be advised to have enough rest, as well as adequate physical activity on a weekly basis. Spasticity in pediatric

cases of MS is most often treated with baclofen or diazepam, botulinum toxin-A, or intense physical therapy (62). Baclofen, a GABA-B agonist, is started at 5–10 mg 3 times a day orally (58). The most common side effects of baclofen therapy are fatigue, seizures, constipation, nausea and vomiting, hallucinations, and hyperthermia (52, 62). Botulinum toxin-A is given at 15–22 U/kg i.m. in children less than 45 kg or 800–12,000 U/kg i.m. in children over 45 kg, every 3–6 months (52).

Current Therapeutic Strategies and Future Directions

The standard first-line therapy of pediatric MS uses different forms of interferon-beta or glatiramer acetate; however, around 30% of pediatric patients with MS discontinue therapy due to side effects, toxicity, persisting relapses, and intolerance or nonadherence. This supports the clear need for new therapeutic strategies. According to the International Pediatric Multiple Sclerosis Study Group (IPMSSG, 71) recommendations, the patients should start first-line immunotherapy (interferon-beta or glatiramer acetate) soon after diagnosis. Patients with poor tolerability or adverse events can be offered to switch the first-line therapy to glatiramer acetate if previously treated with interferon-beta or vice versa. However, these therapies are only partially effective and certain patients may fail to respond. Escalation strategies have demonstrated their benefit in other autoimmune disorders and may also prove to be beneficial in MS. Switching to a second-line therapy should be considered for those patients who do not adequately respond to first-line treatment. The current recommendation involves switching patients to natalizumab or other treatments although these drugs have not been evaluated in children. As in other autoimmune disorders, we need to consider induction therapy at onset. Thus, for patients with severe disease activity at onset, induction therapy with a potent immunosuppressant agent followed by maintenance treatment with interferon-beta or glatiramer acetate may be appropriate.

THE PERSPECTIVE OF DRUG DEVELOPMENT FOR PEDIATRIC MS

According to reference data, there have been no formative clinical drug trials specifically targeting therapy for pediatric MS (72). This is quite unfortunate, considering the vast number of new medications that are becoming available for MS treatment and the incentives available for pharmaceutical agencies willing to undertake pediatric trials. Reasons for the lack of clinical research trials for children could be due to the specific regulations regarding pediatric clinical trials, the off-label use of immunomodulatory medication due to lack of safety and pharmacokinetic data in children, and the number of pediatric patients available for clinic research enrollment.

When conducting future pediatric clinical trials, similar measures as those used in adult trials should be implemented (73). These metrics include relapse rate, time to relapse, and clinical disability with supportive MRI markings. However, there are several additional outcome measures specific for the pediatric population which would be important to incorporate into future clinical trials (74). Quality of life scales would be very important secondary measures in pediatric populations. In addition, cognitive tests are essential, as pediatric MS

has been shown to interfere with cognitive maturation in close to one-third of the children (75). New methods for measuring disability would have to be adjusted in pediatric cases, since most children do not present with measurable physical disability within the first 10 years of the disease. Furthermore, several changes to clinical trial design have been suggested in order to make it more accessible for pediatrics. Designing a trial that cuts down on the number of patients is essential, highlighting the importance of developing international multicentric research and clinical networks. Providing the most successful therapy could also be achieved by deferred treatment/partial crossover, unbalanced arms, and incorporating dose–response studies (72).

The latest study conducted on pediatric-onset MS (POMS) patients with CIS demonstrates the importance of early introduction of DMD on the natural course of the disease (76). This study demonstrated significant reduction in the risk of second attacks, as well as a significant reduction in the risk of worsening in the EDSS and disability rates, in patients who were treated with immunomodulatory therapy early, compared with untreated patients. Most pediatric MS patients experience a second attack between 0.3 and 2.2 years after the first event. In pediatric patients receiving early DMD therapy (before the second attack), there was a 25% reduction of worsening EDSS by the next follow-up. This study, for the first time, consistently supports the beneficial effect of an early DMD exposure in preventing the second attack in CIS and medium- to long-term disability accumulation in POMS.

Conclusion

Pediatric MS is still a challenging diagnostic and therapeutic issue. Advanced MRI techniques (e.g., magnetization transfer, diffusion tensor imaging, and functional MRI) will certainly provide crucial information including cortical involvement in POMS. Possibly they can further explain the different pathophysiological mechanisms of pediatric MS, providing predictive parameters and disease-activity monitoring during different therapeutic protocols (72). Until recently, there have been no randomized controlled clinical trials or safety studies in children with MS (78). According to the US and EU legislation, pediatric studies for new drugs are now required, which have resulted in a notable increase in pediatric studies in the last few years. FDA and EMA encourage a coordinated collaborative approach to product development as an important step toward a more effective product development for children. Nevertheless, the clinicians still have to continue to use new MS drugs in children off-label, since the regulatory authorities have so far not prioritized compounds for potential benefit in children with MS.

Conflict of interest: The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this chapter.

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