Neurotherapeutics (2016) 13:84–95
DOI 10.1007/s13311-015-0396-0

REVIEW

Therapeutic Approach to the Management of Pediatric Demyelinating Disease: Multiple Sclerosis and Acute Disseminated Encephalomyelitis

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Published online: 23 October 2015

Abstract Acquired pediatric demyelinating diseases manifest acutely with optic neuritis, transverse myelitis, acute disseminated encephalomyelitis, or with various other acute deficits in focal or polyfocal areas of the central nervous system. Patients may experience a monophasic illness (as in the case of acute disseminated encephalomyelitis) or one that may manifest as a chronic, relapsing disease [e.g., multiple sclerosis (MS)]. The diagnosis of pediatric MS and other demyelinating disorders of childhood has been facilitated by consensus statements regarding diagnostic definitions. Treatment of pediatric MS has been modeled after data obtained from clinical trials in adult-onset MS. There are now an increasing number of new therapeutic agents for MS, and many will be formally studied for use in pediatric patients. There are important efficacy and safety concerns regarding the use of these therapies in children and young adults. This review will discuss acute management as well as chronic immunotherapies in acquired pediatric demyelination.

Keywords Pediatric multiple sclerosis · Acute disseminated encephalomyelitis · Treatment · Acquired demyelinating syndrome

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Introduction

A first demyelinating attack in childhood or adolescence is known as an acquired demyelinating syndrome (ADS). The course of a first demyelinating attack may be monophasic or may represent the sentinel attack of an underlying, chronic demyelinating disorder such as multiple sclerosis (MS) or neuromyelitis optica (NMO). Pediatric ADS occurs with a reported incidence of 0.5–1.66 per 100,000 children [1–4], and may present as optic neuritis, transverse myelitis, acute disseminated encephalomyelitis (ADEM), or as various other monofocal or polyfocal deficits. In pediatric ADS cohorts, optic neuritis constitutes 22–36 %, transverse myelitis 3–22 %, and ADEM 19–32 % of cases. Other monofocal or polyfocal presentations (21–46 %) comprise the remainder of ADS cases [1–3, 5].

The reported proportion of children with ADS that are ultimately diagnosed with MS is variable and ranges from 15 % to 45 % [2, 3, 6–9]. Up to 10.5 % of all patients with MS experience the clinical onset of MS before the age of 18 years [10]. Though the pathobiology appears similar to that of adult-onset MS, MS in childhood manifests almost exclusively as a relapsing–remitting MS (RRMS) phenotype. When compared with patients with adult-onset MS with similar disease duration, pediatric patients experience a relapse rate 2–3 times higher than that of adults in the first few years of disease [11, 12]. The mechanisms underlying higher relapse rates may conceptually relate to greater immune activation, to differences in the balance of effector and regulatory immune cells, to age-related differences in immune cell access into the central nervous system (CNS), or to intracerebral factors that influence the formation of lesions. Comprehensive, comparative biological studies are required to better understand the impact of age on clinical disease expression. The more inflammatory initial course of pediatric-onset MS highlights

the rationale for prompt initiation of immunomodulatory therapies in children.

There are now 12 Food and Drug Administration (FDA)-approved medications for the treatment of RRMS, with 1 new injectable therapy, 3 oral medications, and 1 infusion therapy approved in the last 5 years. With aims of greater disease suppression comes a higher risk of adverse, and potentially fatal, side effects. Though safety and efficacy data within adult cohorts have been demonstrated, the effects and safety profiles of these new therapies have yet to be determined in pediatric patients.

In this review, we will focus on current diagnostic tools available for differentiating and diagnosing the spectrum of ADS of childhood, with specific attention to that of ADEM and MS. We will review data on the acute care of a demyelinating attack in addition to current and upcoming therapies for MS. Particular attention will be paid to upcoming clinical trials in pediatric MS and the unique obstacles we face as these trials are conceptualized and commenced.

Making a Diagnosis: History, Examination, Laboratory, and Radiologic Evaluation

At initial presentation, there is inherent difficulty in distinguishing monophasic, self-limited ADS from those that will go on to manifest with a chronic neuroinflammatory condition. The International Pediatric MS Study Group (IPMSSG) has proposed consensus guidelines to assist in the diagnosis of the major neuroinflammatory diseases of childhood and supply a common terminology for all providers [13].

ADEM

Polyfocal ADS can manifest with or without encephalopathy. If the patient presents without encephalopathy, a diagnosis of polyfocal clinically isolated syndrome is conferred and the patient is subsequently considered at high risk for going on to meet diagnostic criteria for MS. Children with encephalopathy (mental status changes or behavioral alterations) and concurrent multifocal demyelination, manifesting with polysymptomatic neurologic symptoms, meet diagnostic criteria for ADEM [13]. The differential diagnoses include CNS infection, mitochondrial disease, antibody-associated encephalopathies, and metabolic syndromes.

Patients with ADEM tend to be prepubertal, with 80 % of childhood cases occurring in those aged 10 years or younger. ADEM has a peak incidence at 5–8 years [14–18]. There is a seasonal predilection for fall-to-winter occurrence, and there is often a history of preceding infection or vaccination; however, up to a quarter of cases may lack a clear history of either [17, 19]. There are no current serum or cerebrospinal fluid biomarkers for ADEM; however, cerebrospinal fluid often demonstrates a mild-to-moderate pleocytosis and elevated protein. Oligoclonal bands may be transiently seen in up to 10 % of patients [15, 20]. Autoantibodies, including anti-myelin oligodendrocyte glycoprotein and anti-aquaporin-4, have been reported in children who meet criteria for ADEM, though the exact implications of these antibodies have yet to be fully elucidated [21, 22]. The presence of anti-aquaporin-4 antibodies should prompt consideration of NMO, as the presence of the antibody strongly predicts future relapse.

Typical magnetic resonance imaging (MRI) changes noted in ADEM include multifocal fluid attenuation inversion recovery (FLAIR) and T2-hyperintense lesions that predominately involve the white matter of the brain and spinal cord. Lesions are often large (>1–2 cm) with poorly defined borders. Deep gray matter involvement is often observed. Imaging abnormalities frequently resolve as the patient sustains clinical recovery [8, 15, 17, 18]. Monophasic ADEM, at times, may be difficult to distinguish from the first attack of MS; however, MRI findings of diffuse, bilateral T2-hyperintense lesions in addition to absence of T1-hypointense “black holes” and lack of periventricular lesions weigh heavily in favor of a diagnosis of ADEM [23, 24].

ADEM is most often a monophasic illness and the vast majority of patients make a complete recovery; however, a small subset (6–29 %) of children with an initial diagnosis of ADEM will have future demyelinating attacks characteristic of MS [6, 25]. A small percentage (≤ 10 %) of patients with ADEM will experience a biphasic course, with a subsequent second attack of ADEM—termed multiphasic ADEM [15, 26]. Rarely, ADEM may be followed by monophasic or recurrent optic neuritis and may also precede or follow a diagnosis of anti-N-methyl-D-aspartate (NMDA) receptor encephalitis [27, 28].

MS

MS is characterized by multifocal areas of demyelination within the CNS and by accrual of these lesions over time. By recent diagnostic criteria, MS may be diagnosed at the time of a first clinical attack, as long as imaging at baseline scan demonstrates evidence of “dissemination in time and space” (Fig. 1) [29]. Dissemination in space (DIS) is evidenced by the presence of at least one T2-hyperintense lesion in at least 2 of 4 CNS areas: periventricular, juxtacortical, infratentorial, or spinal cord. Dissemination in time (DIT) is demonstrated at baseline not only by the presence of a clinically silent, enhancing lesion, as well as nonenhancing lesion(s), but may also be confirmed by the appearance of a new T2 or gadolinium-enhancing lesion on follow-up MRI.

Importantly, the use of the 2010 McDonald criteria for MS, when applied at the time of a first attack and single MRI scan, have similar negative and positive predictive values when

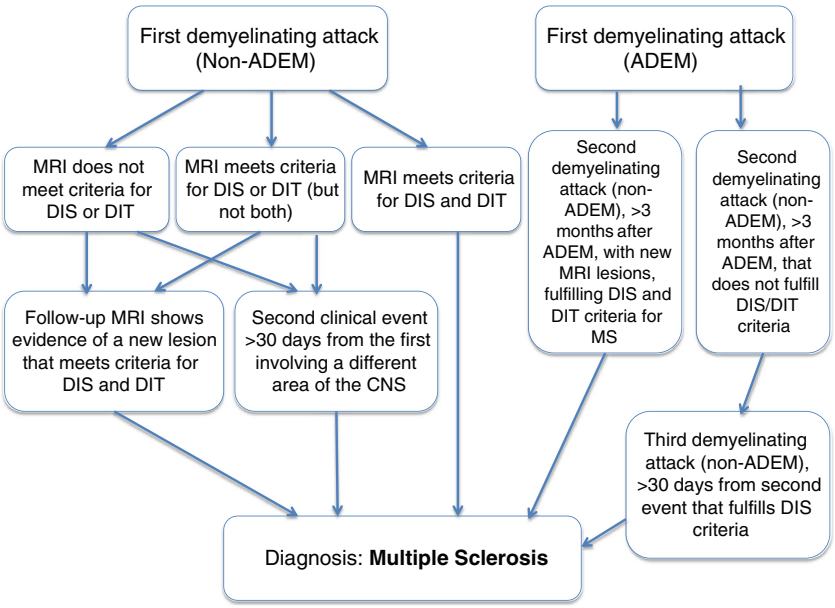

Fig. 1 Algorithm for diagnosis of multiple sclerosis (MS) in a pediatric patient. ADEM = acute disseminated encephalomyelitis; MRI = magnetic resonance imaging DIS = dissemination in space with presence of at least one, T2-hyperintense lesion in at least 2 of the following 4 central nervous system areas: periventricular, juxtacortical, infratentorial, or spinal cord; DIT = dissemination in time demonstrated by new T2 or gadolinium-enhancing lesions on a follow-up MRI compared with a baseline scan or simultaneous asymptomatic gadolinium-enhancing and nonenhancing lesions on a single scan [13, 29]

applied to youth as they do for patients with adult-onset MS. However, application of the 2010 criteria for DIS and DIT at onset in children younger than 11 years of age has a much lower positive predictive value, and thus should be utilized with caution in this context [30]. It is advisable in young children to confirm DIT by serial imaging if diagnostic certainty is in question. Furthermore, the 2010 criteria do not apply in the context of an ADEM presentation (as the high volume of T2 lesions often involves the areas required to fulfill DIS criteria, and variable enhancement of regions that may be considered "asymptomatic" could fulfill DIT criteria).

Figure 1 outlines the means of confirming a diagnosis of MS in pediatric patients with an ADEM-like first attack. Briefly, a diagnosis of MS may be conferred if the child has ≥2 non-ADEM attacks involving different CNS areas separated by at least 30 days or 1 non-ADEM attack >90 days from initial ADEM along with MRI features that meet McDonald 2010 dissemination in time and space criteria [13]. The 90-day consideration was agreed upon by consensus based upon clinical experience in caring for children with ADEM, in whom clinical symptoms of a single event can wax and wane over a period of >30 days.

The likelihood that ADS represents the first attack of MS can be stratified by initial presentation, age of disease onset, and presence of findings on brain MRI. MS risk is influenced by sex, genetic predisposition, and environment. Female sex and an age of disease onset greater than 10 years old at initial ADS are associated with a higher likelihood of MS [6, 25]. An abnormal brain MRI with clinically silent T2-hyperintense and T1-hypointense lesions at the time of first ADS along with the presence of intrathecal synthesis of oligoclonal bands are also associated with a high likelihood of MS [6, 24]. The presence of encephalopathy or a normal brain MRI at the time of ADS (i.e., optic neuritis or transverse myelitis without demyelinating lesions within the brain parenchyma) portends a lower risk of MS [6, 25, 26]. Additionally, the presence of the HLA-DRB1*1501 allele, remote Epstein–Barr virus infection, and low serum vitamin D appear to be predisposing factors for MS [6].

As mentioned above, pediatric patients with MS tend to have a more inflammatory course within the first 2 years of onset [11], manifesting with more frequent clinical relapses and a higher brain T2- and T1-weighted lesion volume [31–34]. Patients with pediatric-onset MS generally maintain good recovery from relapses with minimal-to-no progression in disability within the first 10 years of disease onset; however, irreversible disability and secondary progression ultimately occur at a much earlier age than in adult-onset MS [35]. Despite the lack of early measurable physical disability, cognitive impairment can be noted in up to one-third of pediatric patients with MS [36–38]. Impairments in information processing speed, verbal memory, verbal fluency, and receptive language are seen with resultant negative effects on the patient's scholarship and daily life activities [39]. Longitudinal data are required to determine patterns of cognitive loss or improvement over time, the impact of treatment on cognitive function, and the impact of early-onset MS on academic and vocational achievement into adulthood.

Acute Management of Demyelinating Attacks

Mild symptoms, not impairing daily function, may be sufficiently managed with reassurance, rehabilitation, and ongoing monitoring. For most presentations, intravenous (IV) corticosteroids are considered first-line treatment [40]. Corticosteroids have

been shown to accelerate the speed of recovery in addition to reducing the number of active, gadolinium-enhancing lesions on MRI within a few days post-treatment [41–44]. The putative mechanism of action includes modification of cytokine responses; reduction in T-cell activation; reduction in blood–brain barrier permeability that, in turn, limits extravasation of immune cells into the CNS; and facilitating apoptosis of activated immune cells [45]. International consensus favors doses of 20–30 mg/kg (up to 1 g/day) of IV methylprednisolone daily for 3–5 days. Oral prednisone, starting at 1 mg/kg/day and tapered over 1–4 weeks, is considered for patients with incomplete resolution of symptoms after IV treatment. There is evidence that high-dose oral corticosteroids (1250 mg of prednisone for adults) may be as beneficial as the IV form for treating acute inflammatory, demyelinating attacks of the CNS [46–48]. In children, oral steroids are less commonly used for treating an acute attack as appropriate dosing is unclear.

In cases where steroid therapy is contraindicated or the patient fails to respond adequately to appropriately dosed IV corticosteroids, intravenous immunoglobulin (IVIg) or plasma exchange (PLEX) have been utilized. The benefit of IVIg in acute demyelinating attacks is limited to case reports and small case series [49–53], and is thought to provide benefit by directly affecting cytokine production and T-cell proliferation and by binding potential autoantibodies targeted against myelin [54, 55]. IVIg is given at a dose of 2 g/kg divided over 2–5 days. Side effects include headache, myalgia, fever, and, rarely, aseptic meningitis. Premedication with acetaminophen and diphenhydramine may help reduce infusion-based side effects. There is potential for a severe allergic reaction with IVIg in patients with IgA deficiency; thus, obtaining a serum IgA level prior to initiating treatment is advised. Thromboembolism is another rare side effect associated with IVIg therapy.

PLEX has been used increasingly for treatment of patients with severe or life-threatening demyelination, such as patients with myelitis or brainstem involvement. PLEX is an invasive therapy. Side effects include infection (typically related to the need for an indwelling catheter), alteration of electrolyte profiles, and depletion of coagulation factors. The benefit of PLEX is likely secondary to its therapeutic removal of circulating autoantibodies and immune complexes from the blood. Typical PLEX therapy is 5–7 exchanges over the course of 10–14 days. The benefit of PLEX is likely greatest in a primarily antibody-driven pathology (such as NMO); yet, benefits have been seen in all types of inflammatory disorders, including MS [56, 57].

Comprehensive Management of Pediatric-onset MS

A multidisciplinary team, consisting of neurology, neuropsychology, social work, and physical and occupational therapy, is essential for the care of every pediatric patient with MS. The management of known environmental factors that affect disease course is important. Studies in children have found an association of low serum vitamin D with a heightened risk of developing MS [6], and an increase in relapse rates in patients with confirmed MS [58]. The optimal serum concentration for 25-hydroxyvitamin D remains unknown; however, oral doses of 1000-4000 IU daily in a child to achieve a serum concentration of 30–80 ng/ml is likely appropriate. Second-hand smoke, as a result of parental smoking, appears to increase the risk of developing MS, as does the duration of exposure [59]. In addition, adolescent obesity appears to be associated with an increased risk of subsequent adult-onset MS [60, 61], though the impact of obesity upon established disease is unclear. Thus, family counseling on the importance of diet and lifestyle changes along with cessation of smoking is always indicated.

Currently, there are varied views on the concept of "adequate" disease control in MS. Clinical relapse, reduction in new, T2-bright or gadolinium-enhancing lesions on MRI, and sustained increases in the Expanded Disability Status Scale score are frequently used markers of treatment efficacy. Given the low likelihood of sustained increases in Expanded Disability Status Scale in pediatric MS, only clinical and MRI data were incorporated into the IPMSSG consensus statement, which proposed that an inadequate treatment response in a compliant pediatric patient on full-dose therapy for 6 months be defined as: 1) an increase or lack of reduction in annualized relapse rates (ARR) or new T2 or gadolinium-enhancing lesions on MRI when compared with the pretreatment period; or 2) ≥2 confirmed relapses (as evidenced by clinical or MRI) within a 12-month period or less [40]. As the arsenal of more potent therapies increases, the aims of treatment have shifted towards the potential goal of "no evidence of disease activity"—a metric defined by elimination of clinical relapses, the absence of new/enlarging T2- or gadolinium-enhancing lesions, and lack of increasing sustained disability [62]. The use of "no evidence of disease activity" as a marker of treatment adequacy in children, though provocative and desirable, is a concept that continues to evolve as the treatment landscape of pediatric MS advances.

First-Line Therapies for Pediatric MS

Standard, accepted immunomodulatory therapy in MS, in the form of injections (either subcutaneous or intramuscular), has been commercially available for >20 years. Over time, these therapies have proven to be safe and well-tolerated (Table 1). Additionally, their therapeutic benefits have been shown in multiple adult studies to reduce relapse frequency and decrease accrual of new lesions on MRI. Important aspects of care in using these injectables include patient education on

Table 1 Currently available therapeutic agents for the treatment of relapsing–remitting multiple sclerosis

Medication	Dosing	Side effects	Monitoring*	Pregnancy category
IFN-β1a	22 or 44 μg given SC 3 times weekly (Rebif) OR 30 μg given IM weekly (Avonex) OR 125 μg given SC every other week (Plegridy)	Influenza-like symptoms; headache; injection site reactions; depression; leukopenia; elevated transaminases; thyroid abnormalities	CBC and LFTs monitored every 3–6 months; thyroid function monitored yearly	C
IFN-β1b (Extavia or Betaseron)	0.25 mg given SC every other day	Influenza-like symptoms; headache; injection site reactions; depression; leukopenia; elevated transaminases; thyroid abnormalities	CBC and LFTs monitored every 6 months; thyroid function monitored yearly	C
Glatiramer acetate (Copaxone)	20 mg given SC every other day OR 40 mg given SC 3 times weekly	Injection site tenderness, pruritus, or erythema; lipoatrophy; postinjection systemic reaction	No monitoring required	B
Natalizumab (Tysabri)	300 mg IV infused every 4 weeks	PML; headache; hypersensitivity reaction; transaminase elevation	JC virus antibody and MRI prior to initiation and then every 3–6 months while on therapy; "periodic" CBC and LFTs	C
Fingolimod (Gilenya)	0.5 mg orally daily	First-dose bradycardia; headache; influenza-like symptoms, lymphopenia; elevation of transaminases; reduction in pulmonary FEV; risk of herpes virus infection; macular edema; elevated BP; risk of posterior reversible encephalopathy syndrome; risk of PML	**Pretreatment**: ± ophthalmologic evaluation; CBC, LFTs, bilirubin, EKG, VZV antibody First-dose 6-h bradycardia observation **After initiation**: CBC, LFTs every 3–6 months; ± ophthalmologic examination 3–4 months after starting; BP monitoring at all visits	C
Dimethyl fumarate (Tecfidera)	7 mg or 14 mg orally twice daily	Flushing and gastrointestinal upset; transaminase elevation; eosinophilia; lymphopenia; risk of PML	**Pretreatment**: CBC, LFTs **Post-treatment**: CBC, LFTs every 3–6 months	C
Teriflunomide (Aubagio)	240 mg orally twice daily	Hair thinning; gastrointestinal upset; influenza-like symptoms; peripheral neuropathy; transient acute renal failure and hyperkalemia; leukopenia; severe skin reactions; hepatotoxicity; teratogenicity	**Pretreatment**: pregnancy test; tuberculosis screening; BP, LFTs, CBC **Post-treatment**: every 2–4 weeks LFTs for the first 6 months, periodic BP monitoring	X
Cyclophosphamide (Cytoxan)	Dose titration per patient lymphocyte counts	Nausea/vomiting; susceptibility to infection; amenorrhea; alopecia; hemorrhagic cystitis, infertility, and risk of secondary malignancies	**Pretreatment**: CBC and urinalysis Repeat CBC 7, 14, and 28 days postinfusion; urinalysis with each infusion	D
Rituximab (Rituxan)	375 mg/m^2 weekly for 4 weeks given every 6 months per patient B-cell counts	Infusion reactions; fulminant reactivation of hepatitis B; risk of PML	CBC prior to each course with CBC and B-cell counts weekly to monthly during therapy	C
Alemtuzumab (Lemtrada)	12 mg IV daily for 5 days followed by 12 mg IV daily for 3 days given 1 year after first treatment	Infusion reactions; increased risk of infection; development of secondary malignancy and autoimmune disorders	**Pretreatment**: CBC, creatinine, UA with cell count, thyroid function tests **Post-treatment**: thyroid function every 3 months and CBC, creatinine, UA with cell counts monthly for 48 months after infusion	C

* As countries have variations on recommended monitoring, this section reflects a generalized schematic to monitoring; however, all patients should be monitored according to label/regulatory/local guidelines IFN = interferon; SC = subcutaneously; IM = intramuscularly; CBC = complete blood count with differential; LFT = liver function tests; IV = intravenously; PML = progressive multifocal leukoencephalopathy; JC = John Cunningham; MRI = magnetic resonance imaging; FEV = forced expiratory volume; BP = blood pressure; EKG = electrocardiogram; VZV = varicella zoster virus; UA = urinalysis

administration of the therapy in addition to the general care of injection site reactions should they occur.

It is recognized that adherence to first-line therapy in young patients with MS is not optimal [63, 64]. This, in part, likely relates to the age-appropriate need for autonomy in addition to the social stigma of being diagnosed with a chronic disease at a time where "social camouflage" is a strong desire. For these reasons, it is important to give pediatric patients with MS a sense of control and normalcy by encouraging adherence to therapy but not allowing the therapy to significantly limit their need for independence. The authors' practice is to encourage travel and engagement in collegiate activities, despite the fact that such activities, at times, come at the cost of a single missed dose of therapy.

Retrospective or open-label studies have informed on the safety and efficacy of the current, first-line injectable therapies in children, specifically glatiramer acetate and the interferons (IFNs) (Fig. 2) [40]. At this time, there are no studies available assessing the safety and efficacy of the new oral MS drugs; however, international clinical trials are currently underway.

Glatiramer Acetate

Originally developed to simulate myelin basic protein properties, glatiramer acetate is composed of a mixture of synthetic polypeptides derived from each of 4 amino acids: L-alanine, L-glutamic acid, L-lysine, and L-tyrosine [65]. The mechanism of action is not clear but evidence suggests that it preferentially induces differentiation of CD4+ T cells into T helper 2 cells, thus promoting an anti-inflammatory state. In addition, glatiramer acetate may interact with cytokine-secreting cells prompting a shift from a proinflammatory to a more anti-inflammatory cytokine profile [66, 67].

Glatiramer acetate is given subcutaneously at 20 mg daily or 40 mg thrice weekly. Patients should be educated on common adverse events, including injection site reactions. A transient systemic reaction, occurring within minutes postinjection, is typically associated with shortness of breath, chest pressure, anxiety, and flushing, and can last up to 30 mins. This phenomenon, which often occurs once but can recur with subsequent injections, has been reported in 7–14 % of pediatric patients. Several retrospective studies in pediatric MS have shown this therapy to be well tolerated, with reductions in ARR similar to that reported in adult trials [68–70]. Glatiramer acetate is perhaps the most favored disease-modifying therapy in young women attempting pregnancy, with no known adverse events reported on the fetus [71].

IFN-β

The IFNs are a group of disease-modifying therapies that likely work via several mechanisms including shifting the cytokine balance to a more anti-inflammatory profile and reducing the trafficking of inflammatory cells across the blood–brain barrier [72]. There are 2 subclasses of IFN-β—IFN-β1a and IFN-β1b. IFN-β1a can be given subcutaneously 3 times weekly at a dose of 22 or 44 μg or intramuscularly at a dose of 30 μg weekly. A pegylated version of IFN-β1a is now available and is given at a dose of 125 μg every other week. IFN-β1b is administered subcutaneously at 0.25 mg every other day.

Multiple retrospective studies have demonstrated the safety and efficacy of the IFNs in pediatric MS [68, 69, 73–77]. Potential side effects include influenza-like symptoms (noted in up to 65 % of patients), injection site reactions, elevated transaminases, decreased leukocytes, worsening depression, and headaches. Influenza-like symptoms can often be mitigated with nonsteroidal premedication. Expert opinion suggests that IFNs are better tolerated if they are initiated at 25–50 % of the target dose followed by gradual escalation to full dose over 1–3 months [78]. Fetal exposure to IFN-β *in utero* may be associated with preterm birth and a lower mean birth weight and length [71].

Second-line Therapies for Pediatric MS

When first-line therapies fail to treat a pediatric patient with MS effectively, second-line therapies are often employed. "Failure" of first-line therapies is often secondary to breakthrough disease, poor tolerance/adherence to the therapy, or a combination of both. An estimated 44 % of pediatric patients experience treatment failure with a single first-line therapy. Nearly 80 % of these patients are given a second injectable with a different mechanism of action. The remaining 20 % are offered second-line therapies [79].

The decision to escalate treatment to second-line therapies is not straightforward and remains dependent on several factors, including severity of relapse and degree of recovery from a relapse, safety and adverse event profile of a given treatment option, and the child and family's goals and expectations (Fig. 2). There are currently a handful of therapies utilized for refractory pediatric MS (Table 1). Selection should consider the mechanism of action of a given therapy, the treatment duration required to reach maximal therapeutic benefit, the sustainability of the therapeutic strategy, and the potential effect of the therapy on a young, developing patient's neuroimmunologic system.

Infusion Therapies

Natalizumab

Natalizumab is a monoclonal antibody that is directed against the α-4 subunit of very late activating antigen-4—a cell surface adhesion molecule found on the majority of leukocytes.

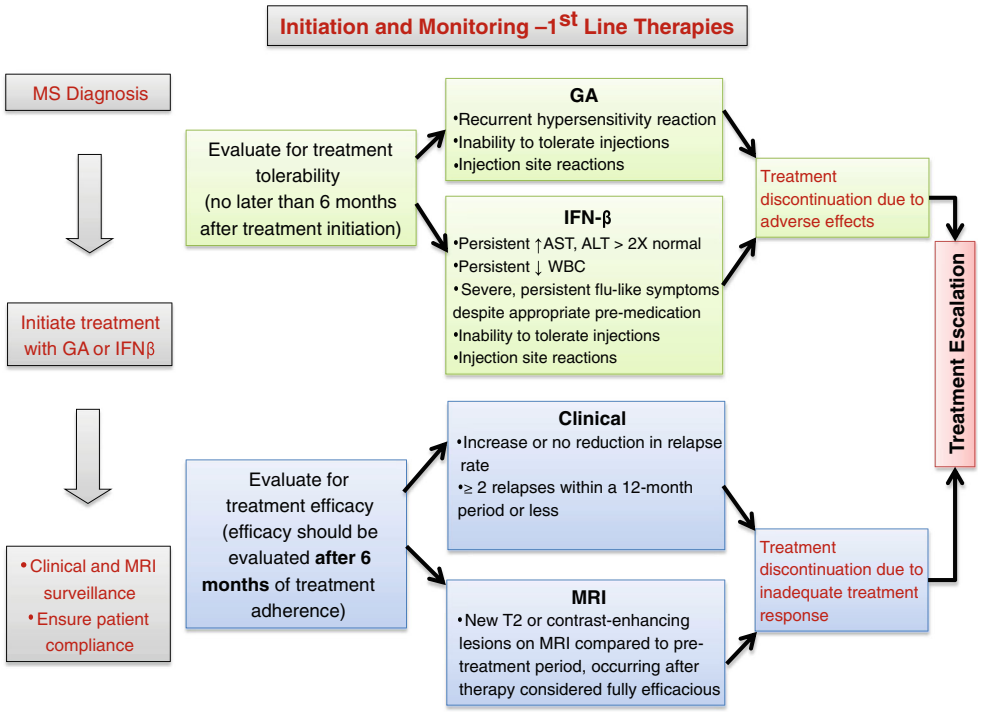

Fig. 2 Proposed algorithm for the approach to treating a pediatric patient with multiple sclerosis (MS) [40]. GA = glatiramer acetate; IFN = interferon; MRI = magnetic resonance imaging; AST = aspartate aminotransferase; ALT = alanine transaminase; WBC = white blood cells

By blocking this integrin's interaction with the vascular endothelium, natalizumab reduces trafficking of immune cells from the periphery into the CNS [80]. Natalizumab is administered as a once-monthly infusion and has demonstrated a high level of efficacy in adults with RRMS; however, the association of natalizumab with progressive multifocal leukoencephalopathy (PML) has limited its use in children and adults. PML is a potentially fatal opportunistic infection of the CNS caused by reactivation of latent John Cunningham (JC) polyomavirus, occurring in immune-suppressed patients. With JC virus infection of oligodendrocytes, cellular lysis occurs and results in widespread, multifocal demyelination [81]. A positive anti-JC virus antibody titer, prior use of immunesuppressant medications, and increased duration of treatment with natalizumab increase the risk of PML [82]. PML risk also appears to correlate directly with anti-JC virus antibody titers [83]. Currently, there are no reported cases of PML secondary to natalizumab use in pediatric patients with MS.

In randomized, placebo-controlled trials in adult MS, comparison of treated patients with those who received placebo revealed an ARR reduction of 68 % over 2 years, sustained reduction in disability progression of 42 %, reduction of new or enlarging T2-hyperintense lesions by 83 %, and reduction in MRI gadolinium-enhancing lesion number by 92 % [84]. A number of cohort studies evaluating the use of natalizumab in pediatric RRMS have demonstrated that natalizumab is well tolerated and appears to reduce ARR effectively, and sustain disability progression, and T2-hyperintense and gadolinium-enhancing lesion accrual [85–91].

Alemtuzumab

Alemtuzumab, a monoclonal antibody directed against CD52, received European Medicines Agency (EMA) approval in 2013 followed by FDA approval in 2014 as therapy for RRMS patients who have inadequately responded to ≥2 MS therapies. A single, 5-day pulse of this treatment rapidly depletes mature, circulating B and T lymphocytes. This depletion is followed by gradual repopulation of these cells over many months, with CD4+ T lymphocytes recovering last. Phase 3 studies in adult RRMS have shown reduction in relapse rates and sustained disability when compared with IFN-β1a [92, 93]. The side effect profile is noteworthy and includes infusion reactions, infection, secondary malignancies, and autoimmune disorders (thyroid disease in up to 34 % of patients, nephropathies in 0.3 %, and immune thrombocytopenia in 1 %) [94]. The safety of this therapy in pediatric MS has not been evaluated.

Cyclophosphamide

Cyclophosphamide is a synthetic anti-neoplastic alkylating agent that interferes with DNA transcription of actively dividing cells. Cyclophosphamide is typically infused monthly (with or without induction) and works as an immunosuppressing agent affecting cytokine expression (with pronounced effects on IL-12) along with T-cell and B-cell function [95]. In adults with RRMS, cyclophosphamide appears to reduce relapse rate and the accrual of new lesions on MRI [96, 97]. A single, multicenter retrospective study of 17 cyclophosphamide-

treated pediatric patients with MS demonstrated improvements in relapse-related neurologic deficits in the acute setting, in addition to decreased relapse rates and stabilization of disability scores 1 year after treatment initiation [98]. The side effect profile of this therapy limits its use in children and includes nausea/vomiting, alopecia, amenorrhea, osteoporosis, hemorrhagic cystitis, and the risk of secondary malignancy and infertility in both males and females.

Mitoxantrone

Mitoxantrone is approved for the treatment of worsening adult RRMS; however, given the risk of cardiotoxicity and high rates of leukemia [99], use of this therapy in pediatric MS is discouraged.

Rituximab

It is now accepted that autoimmune B cells play key roles in establishing MS pathogenesis [100]. A rising interest in the role of humoral immunity occurred when rituximab, a B-cell-depleting drug, was shown to reduce relapse rates and the number of gadolinium-enhancing lesions effectively in patients with RRMS [101]. Rituximab is a chimeric monoclonal antibody against CD20, a protein on the surface of pre-B cells and mature B cells. Two retrospective studies assessing the use of rituximab in children with various neuroinflammatory diseases (including 6 pediatric RRMS cases) showed mixed benefits, with only 3 of the 6 patients with RRMS demonstrating evidence of definite clinical improvement. Infusion-related reactions occurred in 12.5 % [102, 103]. Given these small numbers, more data are needed to determine its utility in the treatment of pediatric MS.

Ocrelizumab

Similar to rituximab, ocrelizumab is a monoclonal antibody directed against CD20; however, while structurally similar to rituximab, this antibody is more humanized than chimeric. A single phase 2 study in adults with RRMS showed significant reductions in gadolinium-enhancing lesions and relapse rates compared with placebo [104]. Phase 3 adult studies are currently underway.

Oral Therapies

Fingolimod

Fingolimod, the first oral drug to receive FDA approval in North America and Europe for adults with RRMS, is a sphingosine-1-phosphate receptor modulator that prevents T-cell egress from peripheral lymphoid tissue into the peripheral and central circulation [105]. Phase 3 studies have shown that fingolimod significantly reduced ARR and MRI activity when compared with placebo and IFN-β1a [106, 107]. Safety issues have been identified, including first-dose bradycardia, the risk of herpes virus dissemination, and macular edema. Three cases of PML in adult patients with RRMS treated with fingolimod (not previously treated with natalizumab) have been reported. The safety in children is unknown, and the effect of fingolimod in patients who are young with active thymic maturation is of concern. A prospective, double-blind, randomized, active-controlled study has begun to evaluate the efficacy and safety of fingolimod *versus* IFN-β1a (30 μg once weekly) in pediatric patients with MS (PARADIGMS), with a primary endpoint of annualized relapse rate reduction.

Dimethyl Fumarate

Dimethyl fumarate is an oral fumaric acid ester that also recently gained FDA approval for the treatment of RRMS in adults. Dimethyl fumarate is thought to work by activating nuclear factor erythroid 2-Y-related factor 2, which thereby upregulates antioxidative pathways and reduces expression of inflammatory cytokines, chemokines, and adhesion molecules [108]. Two phase 3 studies have shown that dimethyl fumarate is effective at significantly reducing relapse rate and the number of new or enlarging T2-hyperintense lesions [109, 110]. Though the safety profile was initially thought to be favorable, other than flushing and gastrointestinal disturbance, reports of PML in the setting of dimethyl fumarate have been released [111, 112]. An open-label, randomized, active-controlled study of dimethyl fumarate *versus* IFN-β1a (30 μg once weekly) in pediatric patients with MS (CONNECT) is currently recruiting. This study's primary endpoint is the proportion of subjects free of new or newly enlarging T2-hyperintense lesions on brain MRI. A randomized, placebo-controlled trial evaluating the efficacy and safety of dimethyl fumarate (IMAGINE) is in development. In this trial, time to first relapse will serve as the primary endpoint. Finally, an open-label study evaluating the effect of dimethyl fumarate on brain MRI lesions in pediatric patients with MS (FOCUS) is actively enrolling.

Teriflunomide

Teriflunomide, an FDA-approved oral therapy for adults with RRMS, reversibly inhibits a key mitochondrial enzyme that is involved in pyrimidine synthesis, required for DNA replication. It is thought that this drug preferentially diminishes activation and proliferation of T- and B-cells (fast-replicating cells) while sparing the proliferation of slow-dividing cells [113]. Studies have shown that teriflunomide significantly reduces relapse rate, disability progression (at higher dose), and MRI evidence of disease activity compared with placebo [114–116]. When looking at risk of treatment failure,

teriflunomide was not statistically superior to IFN-β1a [117]. Hair thinning and gastrointestinal upset are potential side effects in addition to a black box warning, given the potential for hepatotoxicity and teratogenicity. A washout with cholestyramine or activated charcoal is used to hasten removal of teriflunomide in the event of side effects or an unplanned pregnancy. A randomized, double-blind, placebo-controlled trial is currently underway to evaluate the safety and efficacy of teriflunomide in pediatric MS (TERIKIDS), with time to first clinical relapse serving as the primary outcome measure.

Conclusions and Future Directions

The need for prospective, randomized, controlled studies for therapies in pediatric MS is paramount. FDA and EMA regulations mandate the inclusion of a pediatric investigation plan for new therapies in attempts to ensure safe access to the new therapeutic agents for pediatric use. Given the rarity of pediatric MS, international efforts to recruit an adequate number of patients for clinical trials is required. In addition, trial design must consider the number of concurrent trials that can feasibly be launched if target trial enrollment is to be achieved.

Acute management of pediatric ADS is essential to maximize recovery. Consensus definitions for adequate and inadequate disease control in pediatric-onset MS are emerging, and are likely to vary when balancing risks and benefits of different therapies. A rationale and evidence-based strategy for serial therapy selection has yet to be proposed or studied and the cumulative risks of multiple therapeutic exposures remain unknown. The goal of preventing future physical and cognitive disability remains paramount, but long-term observation will be required to determine such outcomes. The IPMSSG (www.ipmssg.org) was formed to help address these priorities.

Compliance with Ethical Standards

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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