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Multiple Sclerosis and Related Disorders (J Graves, Section Editor)

Newer Treatment Approaches in Pediatric-Onset Multiple Sclerosis

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Abstract

Purpose of review With the recognition that pediatric-onset multiple sclerosis (POMS) is characterized by more prominent disease activity, earlier age at onset of disability milestones, and more prominent cognitive impairment compared with physical disability earlier in the disease course compared with adult-onset multiple sclerosis (AOMS), there has been increasing interest in identifying optimal and safe treatment approaches to achieve better disease control in this group. Injectable therapies have been traditionally used as first line in this population, although not formally approved. This review focuses on current treatment and monitoring approaches in POMS.

Recent findings In the past few years, and despite the paucity of FDA-approved medications for use in POMS, an increasing trend toward using newer disease-modifying therapies (DMTs) in this group is observed. However, escalation (as opposed to induction) remains the most frequent approach, and many children continue to be untreated before age 18, particularly before age 12. The only FDA- and EMA-approved disease-modifying therapy in POMS is fingolimod; however, dimethyl fumarate, teriflunomide, natalizumab, ocrelizumab, and alemtuzumab either have been evaluated in observational studies or are being currently investigated in formal randomized controlled trials for use in POMS and appear to be safe in this group. Autologous hematopoietic stem cell transplantation has also been evaluated in a small series. Clinical outcome measures and MS biomarkers have been poorly studied in POMS; however, the use of composite functional scores, neurofilament light chain, optical coherence tomography, and imaging findings is being increasingly investigated to improve early diagnosis and efficient monitoring of POMS.

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Summary Off-label use of newer DMTs in POMS is increasing, and based on retrospective data, and phase 2 trials, this approach appears to be safe in children. Results from ongoing trials will help clarify the safety and efficacy of these therapies in the future. Fingolimod is the only FDA-approved medication for use in POMS. Outcome measures and biomarkers used in AOMS are being studied in POMS and are greatly needed to quantify treatment response in this group.

Introduction

Pediatric-onset multiple sclerosis (POMS), defined as an age at onset younger than 18 years, occurs in approximately 5% of patients with multiple sclerosis (MS) [1]. Several clinical and radiological features distinguish POMS from adult-onset MS (AOMS) which may suggest age-dependent pathophysiological differences. Chronic inflammation in POMS occurs in the setting of the developing central nervous and immune systems, which may explain the differences seen in POMS as compared with AOMS [2•]. Understanding the unique features of the natural history and pathophysiology of POMS is crucial to advance POMS care. The optimal POMS treatment is uncertain in this ever-changing landscape of disease-modifying therapies (DMTs) with diverse mechanism of action that have proven to be effective and safe in the AOMS population. Because of inherent potential differences, safety and efficacy need to be established in POMS.

Conducting clinical trials in the POMS population is challenging given the rarity of the disorder, ethical challenges of pediatric studies, and incomplete knowledge of the natural history of POMS. Legislation in the USA and Europe now mandate pediatric studies for any new biological agent. In December 1998, the FDA issued "the pediatric rule," which requires manufacturers to assess both the safety and efficacy of drugs in children [3]. This rule took effect in April 1999 and was further reenforced in 2001 [4]. Prior to that (during the injectable DMT era), drugs were labeled for use in children without the need for formal clinical trial in this population [4]. Pharmacokinetic studies are required, and safety and efficacy must be established from adult clinical trials before considering studies in children [5]. The need to prioritize randomized controlled trials (RCTs) in POMS has been recently questioned for many reasons. First, from an ethical standpoint, exposing a child with MS to a less effective treatment (comparator) by enrolling him/her in an RCT when other molecules have been proven to be more effective in the adult population is a concern [6]. Second, from a physiological standpoint, even if there are epidemiological, clinical, and radiological differences between POMS and AOMS, there is no clear evidence that POMS is caused by a different pathological process [2•, 6]. Third, the off-label use of newer DMTs in POMS is increasing, and observational studies have shown relatively similar safety and efficacy compared to what is known in AOMS [7••]. Nonetheless, when feasible, establishing the efficacy of DMTs in children and recognizing any side effect difference (for example, the higher rate of seizures seen in the POMS fingolimod trial) are important. Registry studies with longer follow-up times are particularly attractive to observe any unexpected long-term side effect in the youngest patients.

Original platform therapies including interferons and glatiramer acetate have been widely use in POMS, based on observational data (retrospective and open-label studies) [8–14]. Newer DMTs for use in POMS have the potential to better control the disease by addressing the early inflammatory state. This is of particular relevance since POMS patients reach certain levels of disability at an earlier age than people with adult-onset MS, despite the longer time needed to reach these disability milestones [1]. There is hence a compelling need for effective and safe treatment approaches in this group. The aim of this review is to discuss the use of newer treatment approaches in children with MS.

Treatment

Current treatment approaches

Due to the rarity of POMS, the diagnostic challenges of pediatric-onset demyelinating diseases, the paucity of approved medications for treatment of POMS, and the poor understanding of pediatric pharmacokinetics, treatment approaches for POMS tend to favor safer lower-efficacy DMTs [15]. In contrast, AOMS research has grown tremendously in the past decade, and there is a tendency to favor highly effective therapies early on in the course of the disease to avoid disability accumulation, with a goal to achieve no evidence of disease activity, so-called NEDA [16•, 17]. There are many arguments in favor of employing the same approach in POMS [15••]. Clinically, POMS is characterized by a higher number of relapses with better recovery from relapses and longer time to secondary progression and reaching disability milestones (adjusting for disease duration) but an earlier age at onset of disability milestones, more prominent cognitive impairment compared with physical disability earlier in the disease course, and rare progressive course from onset [1, 18–23]. The rate of highly active MS in the pediatric group is high, around 40% in a recent study [24]. People with POMS accumulate a higher number of MRI lesions compared with AOMS, and have more severe axonal damage within acute inflammatory lesions, despite a slower rate of brain atrophy and disability accrual in this population [25, 26]. Moreover, patients with POMS have smaller overall whole brain and thalamic volumes compared with age- and sex-matched controls [27]. These differences highlight the need to target and efficiently control the highly inflammatory disease process in children with MS early in the disease course. Impairment of cognitive function in POMS that is more pronounced than physical disability underscores the detrimental effect of chronic inflammation during neurodevelopment. The high rate of cognitive deficits in POMS also underscores the importance of halting the inflammatory process early to avoid irreversible neurodevelopmental changes [21, 22••].

There are two therapeutic approaches to MS treatment: escalation and early highly effective therapy [28]. The escalation approach involves starting with a safer, lower-efficacy DMT, and switching to a riskier, higher-efficacy DMT when breakthrough disease is observed. This approach has been more widely accepted in POMS, although it is unclear how to define breakthrough disease in this group, and all highly effective DMTs have not been thoroughly studied in POMS (except for fingolimod). Proposed definitions of breakthrough disease from the International Pediatric MS Study Group (IPMSSG) include an increase or no reduction in relapse rate, or new T2 or contrast-enhancing lesions on MRI from pre-treatment period, or ≥ 2 clinical or radiological relapses (clinical or MRI relapses) within < 12 months [29]. The early highly effective therapy approach involves using a higher-efficacy DMT as first-line treatment. Although many studies have suggested that this approach might provide patients with better long-term outcomes, this has not been formally established, even in AOMS [16•]. Ongoing trials aim at answering this question in AOMS (DELIVER-MS, clinicaltrial.gov NCT03535298; TREAT-MS, clinicaltrial.gov NCT03500328).

Current treatment guidelines for POMS are formulated from expert opinion, based on available retrospective observational data, case series, prospective safety data, and rare RCTs. The IPMSSG advised that treatment decisions should

be tailored to each child, and taken after discussing risks and benefits with the patient and the family [30•, 31•]. On May 11, 2018, the FDA has expanded the approval of fingolimod to treat POMS (in children > 10 years) [32]. Before that date, there were no FDA-approved DMT in this group. Interferons and glatiramer acetate are approved by the EMA in children younger than 12 years, along with the recent inclusion of fingolimod. A recent paper from Krysko et al. showed that newer DMTs are frequently used in POMS despite the absence of approved drugs and the limited knowledge on safety and efficacy in this population [7]. In this large cohort from 12 different centers (mean age of onset 13, standard deviation 3.9 years), approximately 79% of patients with clinically definite MS received their first DMT before age 18. Forty-two percent of these patients received a newer DMT before age 18, 17% of whom were prescribed a newer agent as a first-line therapy. Thirty percent of patients with POMS who were initially started on an injectable DMT were switched to a newer DMT before age 18. Expectedly, children started on a newer DMT were older and more disabled at presentation than those started on an injectable drug. The percentage of treated children younger than 12 years was lower in this same cohort: approximately 56% with clinically definite MS were treated with any DMT and only 22% of treated patients received a newer DMT. Since 2012, an increasing trend toward using newer DMTs in POMS was observed [7].

Therapeutic options in POMS

Injectable therapies

Interferons and glatiramer acetate have been extensively used in POMS based on results from observational studies and unblinded RCTs [8, 11–13, 33–36]. They remain the most widely used first-line DMTs in this age group [7]. In 2008–2009, 100% of patients with POMS from a multicenter observational cohort of 1019 patients in the USA were started on an injectable as first-line therapy, while in 2016–2017, only 48% of those ≥ 12 years and 70% of those < 12 years were started on an injectable DMT [7]. The favorable safety profile of these medications in AOMS and data from studies in POMS have supported their use children. Only two POMS trials used a comparator group [8, 33]. Most studies, although limited by their retrospective or unblinded methodology, have shown that interferon and glatiramer acetate are safe and effective in POMS [8, 11, 13, 14, 35]. As in AOMS patients, many POMS patients treated with interferons and glatiramer acetate experience breakthrough disease in our experience.

This review will focus on newer therapies (oral and infusion DMTs). It is important to note that daclizumab has been used off-label in POMS [37], but this medication is no longer available for use in MS and was withdrawn in 2018.

Newer DMTs, mechanisms of actions, dosage, adverse events, and evidence in POMS are shown in Table 1.

Oral therapies

Dimethyl fumarate

Dimethyl fumarate (BG00012, *Tecfidera*®, Biogen) was approved for the treatment of AOMS based on the results of two large RCTs [39, 61]. Current

Table 1. Newer disease-modifying therapies used in pediatric-onset multiple sclerosis

Drug	Evidence in POMS	Route and dosage in POMS	Mechanism of action	Safety Profile
Dimethyl fumarate (*Tecfidera*®, Biogen)	Phase 2 trial [38]	Oral—120 mg bid for 7 days followed by 240 mg bid in phase 2 study and ongoing clinical trials	Activation of the nuclear-factor E2-related factor-2 (Nrf2) transcription pathway and inhibition of NFkB transcription pathway	Facial flushing, gastrointestinal discomfort, rash, malaise, headache, lymphopenia [38–40] PML (6 cases as of January 2019)*
	Retrospective observations [40, 41]	240 mg bid well tolerated in retrospective studies		
	Ongoing phase 3 trials: NCT02283853 (CONNECT), NCT03870763			
Fingolimod (*Gilenya*®, Novartis)	Retrospective observations [24, 42]	0.5 mg once daily	Sphingosine-1-phosphate receptor modulator promotes lymphocyte sequestration in lymph nodes	LFT elevation, chills, cough, headache, leukopenia, URT and LRT infections, herpes viral infections, urinary infections, lymphopenia, macular edema, headache, bradycardia, atrioventricular block, hypertension [43–45] PML (21 cases as of August 2018)**
	Randomized controlled trial (PARADIG*MS*) [43]	0.5 mg once daily, or 0.25 mg once daily for children with body weight ≤ 40 kg		
Teriflunomide (*Aubagio*®, Sanofi Genzyme)	No available data	Oral - 14 and 7 mg in AOMS	Inhibition of dihydroorotate dehydrogenase enzyme, disrupts pyrimidine synthesis, inhibits lymphocyte proliferation	LFT elevation, alopecia, nausea, diarrhea [46, 47] Teratogenic
	Ongoing phase 3 trial: NCT02201108 (TERIKIDS)	Pharmacokinetic run-in determines the 14-mg adult-equivalent dose in TERIKIDS		
Natalizumab (*Tysabri*®, Biogen)	Retrospective and prospective observational studies [48–50]	300 mg IV every 4 weeks	Anti-α4β1-integrin humanized monoclonal antibody, blocks lymphocyte adhesion and entry into CNS	Headache, mild infections, vertigo, gastrointestinal disorders, edema/itching, herpes reactivation, urinary tract infections, fatigue, leukocytosis [48–50]

Table 1. (Continued)

Drug	Evidence in POMS	Route and dosage in POMS	Mechanism of action	Safety Profile
				PML (no pediatric cases reported to date)
Rituximab (*Rituxan®*, Genentech)	Retrospective case series [51, 52] Retrospective observational study [53]	IV 500–1000 mg every 6–12 months IV 1000 mg × 2, 2 weeks apart	Anti-CD20 chimeric monoclonal antibody, depletes B cells	Infusion-related reactions. (headache, chills, rash fever), mild infections (URI, UTI) Anaphylaxis, serious infections (CMV, pneumonia) [51–53]
Ocrelizumab (*Ocrevus®*, Genentech)	No available data Ongoing observational study (NCT03784547)	Initial: IV 300 mg × 2, 2 weeks apart Maintenance: IV 600 mg every 6 months (Adult dosing)	Anti-CD20 humanized monoclonal antibody, depleted B cells	Infusion-related reactions Mild infections (URI, UTI, nasopharyngitis) Herpes reactivation Hepatitis B reactivation Malignancy [54, 55] PML (4 cases to date, not clearly attributed to alemtuzumab)
Alemtuzumab (*Lemtrada®*, Sanofi Genzyme)	No available data Ongoing safety and efficacy clinical trial (NCT03368664, LemKids)	Dose 1: IV 12 mg × 5 days Dose 2: IV 12 mg × 3 days, 1 year from dose 1	Anti-CD52 humanized monoclonal antibody depletes lymphocytes and modulates lymphocyte reconstitution	Infusion-related reactions, infections (mild to serious), malignancy (thyroid, skin, hematologic), autoimmune diseases (thyroid, renal, hematologic) [56, 57] Arterial dissection [58] Intracerebral hemorrhage [59] PML***

*6 adult patients out of > 385,000 treated subjects as of January 31, 2019 (GM personal communication with Biogen)
**21 adult patients out of 254,037 treated subjects as of August 2017 [60]
***4 cases of PML while on Alemtuzumab out of > 18,000 treated subjects as of December 2017, attributed to a carry-over effect from prior DMT use (GM personal communication with Sanofi Genzyme)
AOMS adult-onset multiple sclerosis, *CNS* central nervous system, *IV* intravenous, *LFT* liver function test, *LRT* lower respiratory tract, *PML* progressive multifocal leukoencephalopathy, *POMS* pediatric-onset multiple sclerosis, *URT* upper respiratory tract

evidence in POMS is based on a recently published phase 2 trial and a retrospective review [38]. In their phase 2 trial ($n = 22$), Alroughani et al. report a threefold reduction in new T2 lesions at week 24 compared with pre-treatment baseline. The unadjusted annualized relapse rate was 1.5 in the year prior to study start and 0.8 at 24 weeks. Pharmacokinetics were also evaluated; key pharmacokinetic parameters were estimated with reasonable confidence. The safety profile of dimethyl fumarate in POMS was similar to that observed in AOMS in this study [38]. Another retrospective review of 13 patients in two

US centers, along with a small retrospective study of 9 patients from another center treated with dimethyl fumarate before the age of 18 years, also showed good safety and tolerability data [40, 41].
.An open-label, randomized, multicenter, multiple-dose, active-controlled, parallel-group trial studying the efficacy and safety of dimethyl fumarate, using interferon-β-1a as an active comparator, is currently recruiting patients and the primary completion is expected in September 2020 (CONNECT, ClinicalTrials.gov Identifier: NCT02283853). Another randomized, double-blind, double-dummy, placebo-controlled 3-arm trial aiming on evaluating safety and efficacy of dimethyl fumarate compared with placebo and pegylated interferon-β-1a will start recruitment soon and is expected to end in February 2020 (ClinicalTrials.gov Identifier: NCT03870763).

Fingolimod

Until recently, data on safety and efficacy of fingolimod (*Gilenya®*, Novartis) in POMS was limited to small observational studies [62]. Huppke et al. recently reported results from a retrospective single-center cohort in Germany, showing that patients with POMS treated with fingolimod have a 75% decrease in annualized relapse rate and 81% decrease in new T2 lesions compared to the pre-treatment period which may indicate that the effect of fingolimod is similar if not better in POMS compared to AOMS [24]. Another small observational study from a Brazilian center also highlighted the potential efficacy of fingolimod on highly active POMS (on relapse rate, new T2 lesions, and EDSS) and safety data [42].
Results from a phase 3 randomized, multicenter, double-blind, double-dummy, active-controlled, parallel-group trial (PARADIG*MS*) are now available [43••]. Patients aged 10 to 17 years with a confirmed diagnosis of multiple sclerosis were randomly assigned to receive either oral fingolimod or intramuscular interferon-β-1a for up to 24 months. The primary endpoint was the annualized relapse rate, and secondary endpoints were as follows: the annualized rate of new/enlarging T2 lesions compared with baseline (key secondary endpoint), the time to first confirmed relapse, the percentage of patients who remain relapse-free, the number of gadolinium-enhancing lesions, the volume of enhancing lesions, the percentage of patients free from enhancing lesions, and the safety profile of both active drugs. Many exploratory endpoints were also included. The effect of treatment on the time to 3-month confirmed disability from baseline up to 24 months was also assessed in a post hoc analysis. The mean age of the sample was 15.3 years and mean disease duration since diagnosis was 1.2 years. At the end of the study period, the annualized relapse rate in the fingolimod group was 0.12 versus 0.67 in the interferon group (relative difference, 82%; absolute difference, 0.55 relapses; 95% CI, 0.36 to 0.74; p value < 0.001). There was also a beneficial effect of fingolimod on the key secondary endpoint (annualized rate of new/enlarging T2 lesion, 4.39 with fingolimod vs 9.27 with interferon-β-1a) (relative difference, 53%; absolute difference, 4.88 lesions; 95% confidence interval, 2.91 to 6.84; p value < 0.001), and other secondary endpoints. In a prespecified exploratory analysis, fingolimod was also more effective in decreasing the rate of brain atrophy than interferon-β-1a (– 0.48% with fingolimod vs – 0.80% with interferon). Post hoc analysis showed that fingolimod delayed the time to 3-month confirmed

disability compared with interferon-β-1a (risk reduction, 77.2% over 24 months with fingolimod compared with interferon; hazard ratio, 0.23; 95% confidence interval, 0.08 to 0.66). The overall incidence of adverse events was 88.8% in the fingolimod group and 95.3% in the interferon group. Serious adverse events occurred in 16.8% of patients on fingolimod and 6.5% of patients on interferon. Single cases of second-degree atrioventricular block, and macular edema, among others, were reported in the fingolimod group. There was also an increased risk of seizures in the fingolimod group (six patients (5.6%), two of which categorized as a serious adverse event) compared with the interferon group (one patient (0.9%)). Based on the results of this study, the FDA and EMA have approved the use of fingolimod in POMS in 2018.
As a note, siponimod (*Mayzent®*, Sanofi Genzyme), a selective S1P1 and S1P5 receptor modulator, was approved for relapsing-remitting and secondary progressive AOMS in March 2019 in light of the positive results of a phase 3 RCT, but has not yet been used or studied in POMS [63, 64].

Teriflunomide

Teriflunomide (*Aubagio®*, Sanofi Genzyme) was approved in AOMS based on the results of two placebo-controlled RCTs [46, 47]. There were no differences in treatment failure rate and annualized relapse rate between teriflunomide and interferon-β-1a in adults, which indicated that although newer, teriflunomide has an efficacy similar to the injectable medications [65]. To date, no data is available in POMS. A phase 3, double-blind, randomized, placebo-controlled trial evaluating the efficacy, safety, and pharmacokinetics of teriflunomide in children with relapsing-remitting MS aged 10 to 17 years is currently ongoing (TERIKIDS, ClinicalTrials.gov identifier: NCT02201108) [66]. The completion date is set in November 2019.

Cladribine

Cladribine (*Mavenclad®*, EMD Serono) was approved for the treatment of relapsing-remitting and active secondary progressive AOMS in March 2019 following two RCTs (CLARITY and ORACLE-MS), and is recommended for patients who have had an inadequate response to or did not tolerate an alternate DMT [67–69]. It has not yet been studied in POMS.

Infusion therapies

Natalizumab

Natalizumab (*Tysabri®*, Biogen) has shown robust effects on relapse rate reduction, disability progression, and new lesion formation compared with placebo and with interferon-β-1a in AOMS [70–72]. In POMS, while there are no RCTs evaluating natalizumab, there have been observational studies (REF), the largest of which included 101 POMS patients from an Italian registry (mean age of onset 12.9 years, mean EDSS 2.6, prior use of DMT in 66%, and mean treatment duration on natalizumab 34.2 months) [48].

The annualized relapse rate decreased from a mean of 2.3 to 0.1 following initiation of natalizumab, and there was a significant reduction in contrast-enhancing lesions on brain MRI [48]. These observations were consistent with results from other studies [49, 50, 73, 74].

Natalizumab was found to be well tolerated and safe in the POMS patients. In some studies, no clinical adverse events were experienced [49, 74]. Even though progressive multifocal leukoencephalopathy (PML) has not been reported in POMS patients on natalizumab, it is important to establish John Cunningham virus (JCV) serostatus prior to initiating therapy. In healthy pediatric population, JCV seropositivity was 21%, which is lower than that of the healthy adult population [75]. The prevalence of JCV seropositive appears to be higher in POMS as compared with the general healthy pediatric population, ranging from 39 to 51.6% [48, 49, 76]. Nevertheless, these rates are still lower than the rate of JCV seropositivity in AOMS patients [77]. Long-term safety of natalizumab with regard to PML risk is unclear in POMS.

While tolerability and safety data are reassuring based on published observational studies, long-term safety of natalizumab in children is not known. Larger studies are needed to confirm previous findings, especially for PML risk. There are two ongoing studies of natalizumab in POMS. One is a phase 1, multicenter, open-label, single-arm, pharmacokinetic study of natalizumab in 13 POMS patients (NCT01884935); the second is an observational study involving 400 POMS patients (NCT02137109).

Rituximab

Rituximab (*Rituxan®*, Genentech) is used to treat a variety of autoimmune and paraneoplastic conditions in adults. Rituximab is not FDA approved to treat MS. Though there were promising phase II trials, a phase III program was not pursued. Off-label use is common. Its tolerability and efficacy were demonstrated in several phase I/II trials and observational studies in AOMS [78–80]. In POMS, rituximab is one of the most commonly used DMTs and is increasing in frequency along with other newer DMTs [7]. A retrospective case series of 14 POMS treated with IV rituximab 500–1000 mg every 6 to 12 months (median length of treatment 23.6 months) reported no relapses and no EDSS worsening during duration of treatment [51]. In another retrospective case series of 11 patients with CNS inflammatory diseases, two of whom had RRMS and 1 SPMS, IV rituximab was administered 1000 mg twice 2 weeks apart. Two patients reported reduction in relapse rate post-infusion while one patient switched therapies due to continued relapses [52].

Depletion of peripheral B cells usually occurs after the second week of infusion and persists for at least 24–48 weeks. Safety data from aforementioned case series reported similar outcomes in POMS [51, 52]. A large cohort of 144 pediatric patients with neuroinflammatory or autoimmune diseases (4 with POMS) evaluated safety and tolerability of rituximab [53]. In this study, most patients tolerated the infusions well; common adverse reactions were infusion-related reactions and mild infectious events. However, more serious adverse events were also reported including anaphylaxis (2%), serious disabling infections (1.4%), and death (1.4%). Younger

patients (< 5 years old) had similar hematologic and immunologic effects compared to older patients except higher incidence of hypogammaglobulinemia (28% vs 19%) [53]. No rituximab-related PML cases were reported in POMS.
Despite reports of improved clinical and radiographic outcomes of rituximab use in POMS, caution should be practiced when prescribing rituximab, after carefully weighing the risks.

Ocrelizumab

Ocrelizumab (*Ocrevus*®, Genentech) is FDA approved to treat relapsing or primary progressive MS in adults. It differs from rituximab in that it is fully humanized and binds to a different but overlapping epitope on CD20. Pivotal trials in AOMS demonstrate significant reductions in annualized relapse rate, delay of disability progression, and reductions in MRI outcomes [54, 55]. Available safety and tolerability data were favorable in ocrelizumab-treated populations. B cell depletion is achieved by week 2 following the initial infusion and persists for 72 weeks [54, 55].
Currently there are no published reports of ocrelizumab use in POMS. However, based on positive experiences with rituximab, and the high efficacy and tolerability of ocrelizumab demonstrated in AOMS, ocrelizumab use may become more frequent in POMS. There is an ongoing retrospective observational study involving both AOMS and POMS on epidemiological data regarding ocrelizumab use in Latin America (NCT03784547).

Alemtuzumab

Alemtuzuab (*Lemtrada*®, Sanofi Genzyme) was FDA approved to treat RRMS in adults in 2014 after demonstrating significant reductions in relapse rate, disability progression, and brain atrophy as a first-line and second-line agent in pivotal trials [56, 81]. Many patients experienced sustained effects against disease activity even on 5-year follow-ups [57].
There are no current studies of alemtuzumab in POMS. An ongoing company-sponsored multicenter open-label trial aimed to study safety and efficacy of alemtuzumab is recruiting POMS patients who are 10–18 years old with RRMS who have failed at least 2 DMTs (NCT03368664).
Safety data in alemtuzumab in pediatric patients are from studies in transplant recipients where alemtuzumab was used as an immunoablative induction therapy, and results report mild to serious infectious complications [82–84]. In AOMS, more concerning side effects include autoimmune diseases, cancers, and recent reports of arterial dissection and intracerebral hemorrhage [59]. Therefore, despite its high efficacy, alemtuzumab use in POMS should undergo careful considerations of risk analysis.

Stem cell therapies

While DMTs focus on immunomodulation, cell-based therapies have generated interest in the treatment of MS due to their ability to regenerate various cell types, modulate immune response, and promote repair. Several cell-based

therapies have been evaluated in MS.

Hematopoietic stem cells

The rationale for autologous hematopoietic stem cell transplantation following immunoablation (I/AHSCT) is the concept of "resetting" the immune system with intensive depletion of the current autoreactive immune system and reconstituting a system with more balanced immunoregulatory functions. MS patients following I/AHSCT were found to have circulating T cells with altered clonal profile [85, 86]. Several case series involving RRMS and SPMS demonstrated that I/AHSCT were effective in producing a sustained effect in disease activity and progression [87]. Recent phase II trials have also demonstrated efficacy in MRI outcomes and clinical disease activity; the results were more pronounced in patient with active inflammation [87].

There are currently no clinical trials on I/AHSCT in POMS. An observational study of 21 POMS patients from the European Society for Blood and Marrow Transplantation registry who received intensive I/AHSCT included children with age range 9–18 years at the time of transplant, average pre-transplant EDSS 6, annualized relapse rate 3, contrast-enhancing lesions 2, and median follow-up time 2.8 years. Post-transplant, no patients experienced worsening in EDSS, and 16 patients had improvements in EDSS. Nineteen patients remained relapse free, and 15/18 patients with MRI data remained MRI activity free (with sustained effects > 10 years). In terms of safety, there was no increased incidence of adverse events compared with those reported in adults, and specifically no treatment-related mortality. One patient required intensive care for pseudomonas sepsis and 2 had fever with bacteremia [88•].

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are pluripotent precursor cells derived from the mesodermal cell line (bone marrow and adipose tissue) and have high degree of plasticity. They have wide range of immunomodulatory, repair, and neuroprotective properties [89]. Numerous phase I clinical trials in AOMS have demonstrated feasibility of MSC transplantation via intravenous or intrathecal routes. These studies have also demonstrated safety and tolerability of MSC transplantation with no serious adverse reactions [90]. There are currently no reported cases or trials of MSC use in POMS.

Outcome measures in POMS

The identification of clinically meaningful outcome measures to assess treatment response in MS is challenging. Such tools are needed to assess the efficacy of new drugs in clinical trials and to monitor treatment response in each patient in routine clinical practice. In the clinical setting, an outcome measure must be easy to use, clinically useful, and readily interpretable [91]. The ultimate goal of treatment is theoretically to achieve NEDA, defined as the complete absence of identifiable disease activity (clinical relapses, MRI activity, disability progression, and brain atrophy) [17]. However, it currently appears to be an unrealistic goal, since no DMT has been shown to achieve long-term complete NEDA [92].

In a 7-year longitudinal adult MS cohort, NEDA was achieved in 7.9% of patients only [92]. The use of NEDA as an outcome measure has not been studied in POMS. Due to the higher rate of clinical and radiological activity in children with MS, achieving an activity-free disease status is challenging. A less stringent description of breakthrough disease in POMS was defined in a consensus statement by the IPMSSG in 2012 as the absence of reduction in relapse rate or new T2 or gadolinium-enhancing lesions compared with the pretreatment period, or two or more confirmed clinical or radiological relapses within a 12-month period in a patient with optimal compliance on his treatment for at least 6 months [29].

Disability scores that reliably evaluate longitudinal neurological function have been extensively studied in AOMS. The Expanded Disability Status Scale (EDSS), the most commonly used clinical outcome measure, relies strongly on ambulation status and has been criticized for poorly capturing other functional systems contributing to overall disability [93–95]. As previously discussed, physical disability, particularly gait impairment, is less prominent in POMS. Patients with POMS take longer time to reach disability milestones than patients with AOMS (23.8 vs 15.5 years to reach an EDSS of 4 in one study) [20]. In another study, the annualized relapse rate was 2.3 times higher in POMS compared to AOMS despite similar EDSS scores between the two groups over a period of 6 years, and the relapse rate during the first 5 years of POMS did not affect EDSS scores at year 5 [19]. Finally, a longitudinal study of patients with POMS treated with interferons or glatiramer acetate showed that EDSS scores remained unchanged after a mean treatment duration of 53.6 to 74.6 months on injectable therapies compared with baseline [36]. Hence, the EDSS might not be a sensitive measure in POMS, especially early in the disease [96••]. The Multiple Sclerosis Functional Composite (MSFC) score is an established tool evaluating walking (using the timed 25-ft walk test), hand function (using the 9-hole peg test), and cognition (classically using the paced auditory serial addition test (PASAT), although the symbol-digit modalities test (SDMT) is increasingly used instead) and low-contrast visual acuity test. The MSFC has been used to comprehensively evaluate neurological function in AOMS for the past 20 years with limited use in POMS [97, 98]. Waldman et al. suggested a modified version of the MSFC, which includes the SDMT instead of the Children's PASAT and the more stringent 1.25% low-contrast visual acuity test, as a more sensitive tool than the traditional MSFC to capture subtle impairments in POMS [96••].

Newer biomarkers that can serve as surrogates of disease activity, treatment response, and neurodegeneration are being extensively studied in AOMS with more limited studies in POMS. For example, serum and CSF neurofilament light chain (NfL) have been increasingly studied in AOMS and appear to be associated with disease activity and treatment response [99]. In children with clinically isolated syndrome, CSF NfL levels are associated with a diagnosis of clinically definite MS. [100••] CSF NfL levels might also be helpful in differentiating ADEM from MS. [101] Serum NfL seem to be correlated to treatment response in POMS [102]. More research is needed to better understand the role of NfL as a biomarker of pediatric demyelinating disorders. Another example is the

use of optical coherence tomography (OCT) as a marker of neurodegeneration. In adults, there is increasing evidence that measuring retinal nerve layer and ganglion cell layer thickness is a valuable tool to reflect neurodegeneration and evaluate drugs with a neuroprotection potential [103]. To date, longitudinal studies using OCT in POMS are lacking, and its role in this group is unclear. Retinal atrophy occurs early in POMS and is seen in children without a prior history of optic neuritis, as in adults [104, 105]. However, it remains unclear how to interpret retinal layers thickness changes in children (even healthy controls), since orbital size and possibly retinal layers thickness increase as children grow and myopia can influence RNFL thickness, which can mask retinal degeneration in younger patients [103].

Other novelties in POMS

Diagnostic challenges and advances

The diagnosis of POMS can be challenging. Previous research evaluating the applicability of the 2005 and 2010 McDonald criteria in children has shown that those criteria, although helpful in the diagnosis of POMS, have to be considered with caution in children younger than 11 years old and in children with acute disseminated encephalomyelitis (ADEM)–like presentations [106]. In the recent 2017 revisions of the McDonald criteria, the panel emphasize the importance of excluding alternative diagnosis (specifically neuromyelitis optica spectrum disorders and myelin oligodendrocyte glycoprotein antibody–related disorders) before confirming the diagnosis of POMS, and the usefulness of identifying oligoclonal bands in the CSF to support the diagnosis [107]. In 2013, the IPMSSG published criteria for POMS, ADEM as a first manifestation of MS, and multiphasic ADEM [108]. A detailed discussion on the diagnostic criteria of POMS is out of the scope of this review; however, a mention should be made on role of the central vein sign in the early diagnosis of MS. In AOMS, the presence of a vein in the center of a lesion is increasingly recognized as an early diagnostic marker of MS. In a AOMS study, all patients had a central vein sign in > 40% of their lesions [109]. In a study of 26 POMS, all had at least one lesion containing a central vein, while 81% had at least two and 65% had at least three lesions containing a central vein, and 65% had > 40% perivenular lesions [110]. It remains unclear if a central vein sign can discriminate monophasic ADEM from MS. [111, 112]

Compliance to therapy in children and adolescents

Adherence to DMTs is an important determinant of treatment efficacy in real-world clinical settings. The rates of non-adherence appear to be high in POMS and increase with disease duration [113]. Adolescents in particular have difficulties accepting the long-term benefit of chronic therapies [113]. Numerous psychosocial factors influence adherence, including cognitive function, psychiatric comorbidities, socio-economic status, peer support, and level of physical disability [113–116]. In children and adolescents with MS, self-reported physical function was associated with better adherence to

DMTs [117]. Parental involvement is associated with poorer subjective measures of cognitive functioning [117]. Novel objective measures of compliance exist but are not infallible. For example, electronic pill bottles that record the number of times the bottle was opened do not directly reflect pill ingestion, and electronic devices have been associated with poorer adherence and increased parental involvement [117, 118]. Patients and/or parent recorded logs can help with compliance to some extent, but do not necessarily reflect actual adherence. For these reasons, it is important for health care professional to inquire about treatment compliance and address the reasons of non-adherence in POMS.

Conclusions

The current treatment approach of AOMS leans toward optimal disease control early in the course of MS which might have the potential to achieve better long-term outcomes, although real-word evidence that suggest using first-line high-efficacy DMTs is lacking. Recognizing that POMS is associated with more prominent clinical and radiological activity, earlier age at onset of disability milestones, and a risk of earlier cognitive impairment, there is a need to evaluate high-efficacy DMTs in this sub-group as well. Off-label use of newer DMTs in POMS is increasing, and based on retrospective studies, case series, and phase 2 trials, this approach appears to be safe in children. More data are needed before standardizing the use of first-line newer therapies in POMS, and ongoing trials will help clarify this approach. Fingolimod is the only FDA-approved medication for use in POMS at this moment. Better outcome measures are also needed to quantify treatment response in this group, and efforts to understand the applicability and optimize traditionally used tools in AOMS are ongoing. This also applies to recently developed biomarkers, such as NfL and central vein sign on MRI.

Compliance with Ethical Standards

Conflict of Interest

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Renoux C, Vukusic S, Mikaeloff Y, Edan G, Clanet M, Dubois B, et al. Natural history of multiple sclerosis with childhood onset. N Engl J Med. 2007;356(25):2603–13.
2.• Bar-Or A, Hintzen RQ, Dale RC, Rostasy K, Brück W, Chitnis T. Immunopathophysiology of pediatric CNS inflammatory demyelinating diseases. Neurology. 2016;87(9):S12–9

Recent comprehensive review on the physiopathology of pediatric-onset demyelinating diseases.

3. Regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients–FDA. Final rule. Fed Regist. 1998;63(231):66631–72.
4. Steinbrook R. Testing medications in children. N Engl J Med. 2002;347:1462–70.
5. Chitnis T. Disease-modifying therapy of pediatric multiple sclerosis. Neurotherapeutics. 2013;10(1):89–96.
6. Ghezzi A. Randomized clinical trials (RCTs) in pediatric multiple sclerosis: are they really necessary? Mult Scler. 2017;23(7):1042–3.
7.•• Krysko KM, Graves J, Rensel M, Weinstock-Guttman B, Aaen G, Benson L, et al. Use of newer disease-modifying therapies in pediatric multiple sclerosis in the US. Neurology. 2018;91(19):e1778–87

Important analysis on trends in using newer disease-modifying therapies in pediatric-onset multiple sclerosis.

8. Mikaeloff Y, Caridade G, Tardieu M, Suissa S. Effectiveness of early beta interferon on the first attack after confirmed multiple sclerosis: a comparative cohort study. Eur J Paediatr Neurol. 2008;12(3):205–9.
9. Banwell B, Schelensky L, Reder AT, Antonijevic I, Alexey B, Eraksoy M, et al. Safety and tolerability of interferon beta-1b in pediatric multiple sclerosis. Neurology. 2006;66(4):472–6.
10. Krupp LB, Pohl D, Ghezzi A, Boyko A, Tenembaum S, Chen L, et al. Subcutaneous interferon β-1a in pediatric patients with multiple sclerosis: regional differences in clinical features, disease management, and treatment outcomes in an international retrospective study. J Neurol Sci. 2016;363:33–8.
11. Mikaeloff Y, Moreau T, Debouverie M, Pelletier J, Lebrun C, Gout O, et al. Interferon-beta treatment in patients with childhood-onset multiple sclerosis. J Pediatr. 2001;139(3):443–6.
12. Tenembaum SN, Segura MJ. Interferon beta-1a treatment in childhood and juvenile-onset multiple sclerosis. Neurology. 2006;67(3):511–3.
13. Pohl D, Rostasy K, Gärtner J, Hanefeld F. Treatment of early onset multiple sclerosis with subcutaneous interferon beta-1a. Neurology. 2005;64(5):888–90.
14. Kornek B, Bernert G, Balassy C, Geldner J, Prayer D, Feucht M. Glatiramer acetate treatment in patients with childhood and juvenile onset multiple sclerosis. Neuropediatrics. 2003;34(3):120–6.
15.•• McGinley M, Rossman IT. Bringing the HEET: the argument for high-efficacy early treatment for pediatric-onset multiple sclerosis. Neurotherapeutics. 2017;14(4):985–98

Discussion on escalation vs. induction approach in pediatric-onset multiple sclerosis.

16.• Brown JWL, Coles A, Horakova D, Havrdova E, Izquierdo G, Prat A, et al. Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis. JAMA. 2019;321(2):175–87

Recent publication on the potential benefit of induction approach on long-term outcomes in adults with multiple sclerosis.

17. Bevan C, Cree BA. Disease activity free status: a new end point for a new era in multiple sclerosis clinical research? JAMA Neurol. 2014;71(3):269–70.
18. Gorman MP, Healy BC, Polgar-Turcsanyi M, Chitnis T. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. Arch Neurol. 2009;66(1):54–9.
19. Benson LA, Healy BC, Gorman MP, Baruch NF, Gholipour T, Musallam A, et al. Elevated relapse rates in pediatric compared to adult MS persist for at least 6 years. Mult Scler Relat Disord. 2014;3(2):186–93.
20. Harding KE, Liang K, Cossburn MD, Ingram G, Hirst CL, Pickersgill TP, et al. Long-term outcome of paediatric-onset multiple sclerosis: a population-based study. J Neurol Neurosurg Psychiatry. 2013;84(2):141–7.
21. Amato MP, Goretti B, Ghezzi A, Lori S, Zipoli V, Moiola L, et al. Cognitive and psychosocial features in childhood and juvenile MS: two-year follow-up. Neurology. 2010;75(13):1134–40.
22.•• Ruano L, Branco M, Portaccio E, Goretti B, Niccolai C, Patti F, et al. Patients with paediatric-onset multiple sclerosis are at higher risk of cognitive impairment in adulthood: an Italian collaborative study. Mult Scler. 2018;24(9):1234–4.

Recent study on the prevalence of cognitive impairment in pediatric multiple sclerosis compared with adult multiple sclerosis.

23. Alroughani R, Ahmed SF, Al-Hashel J. Pediatric-onset multiple sclerosis disease progression in Kuwait: a retrospective analysis. Pediatr Neurol. 2015;53(6):508–12.

24.•• Huppke P, Huppke B, Ellenberger D, Rostasy K, Hummel H, Stark W, et al. Therapy of highly active pediatric multiple sclerosis. Mult Scler J. 2019;25(1):72–8.

Important paper on the prevalence of highly active disease in pediatric multiple sclerosis and benefit of natalizumab and fingolimod in this group.

25. Yeh EA, Weinstock-Guttman B, Ramanathan M, Ramasamy DP, Willis L, Cox JL, et al. Magnetic resonance imaging characteristics of children and adults with paediatric-onset multiple sclerosis. Brain. 2009;132(Pt 12):3392–400.
26. Pfeifenbring S, Bunyan RF, Metz I, Rover C, Huppke P, Gartner J, et al. Extensive acute axonal damage in pediatric multiple sclerosis lesions. Ann Neurol. 2015;77(4):655–67.
27. Kerbrat A, Aubert-Broche B, Fonov V, Narayanan S, Sled JG, Arnold DA, et al. Reduced head and brain size for age and disproportionately smaller thalami in child-onset MS. Neurology. 2012;78(3):194–201.
28. Rieckmann P. Concepts of induction and escalation therapy in multiple sclerosis. J Neurol Sci. 2009;277(S1):S42–5.
29. Chitnis T, Tenembaum S, Banwell B, Krupp L, Pohl D, Rostasy K, et al. Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis. Mult Scler. 2012 Jan;18(1):116–27.
30.• Wassmer E, Chitnis T, Pohl D, Amato MP, Banwell B, Ghezzi A, et al. International Pediatric MS Study Group Global Members Symposium report. Neurology. 2016;87(9):S110–.

Expert consensus on advances and challenges in the diagnosis and management of pediatric multiple sclerosis and other neuroinflammatory CNS disorders.

31.• Chitnis T, Ghezzi A, Bajer-Kornek B, Boyko A, Giovannoni G, Pohl D. Pediatric multiple sclerosis: escalation and emerging treatments. Neurology. 2016;87(S2):S103–.

Review on different treatment approaches and evidence in pediatric multiple sclerosis.

32. Food and Drug Association. Press Announcements - FDA expands approval of Gilenya to treat multiple sclerosis in pediatric patients. Office of the Commissioner; 2018 [cited 2019 Mar 31]. Available from: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm607501.htm.
33. Pakdaman H, Fallah A, Sahraian MA, Pakdaman R, Meysamie A. Treatment of early onset multiple sclerosis with suboptimal dose of interferon beta-1a. Neuropediatrics. 2006;37(4):257–60.
34. Ghezzi A, Amato MP, Capobianco M, Gallo P, Marrosu G, Martinelli V, et al. Disease-modifying drugs in childhood-juvenile multiple sclerosis: results of an Italian co-operative study. Mult Scler. 2005;11(4):420–4.
35. Tenembaum SN, Banwell B, Pohl D, Krupp LB, Boyko A, Meinel M, et al. Subcutaneous interferon beta-1a in pediatric multiple sclerosis: a retrospective study. J Child Neurol. 2013;28(7):849–56.
36. Ghezzi A, Amato MP, Annovazzi P, Capobianco M, Gallo P, La Mantia L, et al. Long-term results of immunomodulatory treatment in children and adolescents with multiple sclerosis: the Italian experience. Neurol Sci. 2009;30(3):193–9.
37. Gorman MP, Tillema J-M, Ciliax AM, Guttmann CRG, Chitnis T. Daclizumab use in patients with pediatric multiple sclerosis. Arch Neurol. 2012;69(1):78–81.
38. Alroughani R, Das R, Penner N, Pultz J, Taylor C, Eraly S. Safety and efficacy of delayed-release dimethyl fumarate in pediatric patients with relapsing multiple sclerosis (FOCUS). Pediatr Neurol. 2018;83:19–24.
39. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012;367(12):1087–97.
40. Rossman I, Moodley M, Rensel M. Dimethyl fumarate is well tolerated in a small cohort of pediatric-onset multiple sclerosis patients (P3.010). Neurology. 2016;86(16 Supplement):3.010.
41. Makhani N, Schreiner T. Oral dimethyl fumarate in children with multiple sclerosis: a dual-center study. Pediatr Neurol. 2016;57:101–4.
42. Fragoso YD, Alves-Leon SV, Barreira AA, Callegaro D, Brito Ferreira ML, Finkelsztejn A, et al. Fingolimod prescribed for the treatment of multiple sclerosis in patients younger than age 18 years. Pediatr Neurol. 2015;53(2):166–8.
43.•• Chitnis T, Arnold DL, Banwell B, Brück W, Ghezzi A, Giovannoni G, et al. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. N Engl J Med. 2018;379(11):1017–2.

Pivotal trial of fingolimod in pediatric multiple sclerosis, leading to FDA and EMA approval of this drug in children.

44. Kappos L, Radue E-W, O'Connor P, Polman CH, Hohlfeld R, Calabresi PA, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010;362(5):387–401.
45. Soelberg Sorensen P. Safety concerns and risk management of multiple sclerosis therapies. Acta Neurol Scand. 2017;136(3):168–86.
46. O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med. 2011;365(14):1293–303.
47. Confavreux C, O'Connor P, Comi G, Freedman MS, Miller AE, Olsson TP, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13(3):247–56.
48. Ghezzi A, Moiola L, Pozzilli C, Brescia-Morra V, Gallo P, Grimaldi LME, et al. Natalizumab in the pediatric MS population: results of the Italian registry. BMC Neurol. 2015;15:174.
49. Ghezzi A, Pozzilli C, Grimaldi LME, Moiola L, Brescia-Morra V, Lugaresi A, et al. Natalizumab in pediatric multiple sclerosis: results of a cohort of 55 cases. Mult Scler. 2013;19(8):1106–12.

50. Kornek B, Aboul-Enein F, Rostasy K, Milos R-I, Steiner I, Penzien J, et al. Natalizumab therapy for highly active pediatric multiple sclerosis. JAMA Neurol. 2013;70(4):469–75.
51. Salzer J, Lycke J, Wickstrom R, Naver H, Piehl F, Svenningsson A. Rituximab in paediatric onset multiple sclerosis: a case series. J Neurol. 2016;263(2):322–6.
52. Beres SJ, Graves J, Waubant E. Rituximab use in pediatric central demyelinating disease. Pediatr Neurol. 2014;51(1):114–8.
53. Dale RC, Brilot F, Duffy LV, Twilt M, Waldman AT, Narula S, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology. 2014;83(2):142–50.
54. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung H-P, Hemmer B, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med. 2017;376(3):221–34.
55. Montalban X, Hauser SL, Kappos L, Arnold DL, Bar-Or A, Comi G, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med. 2017;376(3):209–20.
56. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomized controlled phase 3 trial. Lancet. 2012;380(9856):1829–1839.
57. Havrdova E, Arnold DL, Cohen JA, Hartung H-P, Fox EJ, Giovannoni G, et al. Alemtuzumab CARE-MS I 5-year follow-up: durable efficacy in the absence of continuous MS therapy. Neurology. 2017;89(11):1107–16.
58. Durand-Dubief F, Marignier R, Berthezene Y, Cottin J, Nighoghossian N, Vukusic S. Spontaneous multiple cervical artery dissections after alemtuzumab. Mult Scler. 2019. https://doi.org/10.1177/1352458519828663.
59. Azevedo CJ, Kutz C, Dix A, Boster A, Sanossian N, Kaplan J. Intracerebral haemorrhage during alemtuzumab administration. Lancet Neurol. 2019;18(4):329–31.
60. Ontaneda D, Moore A, Bakshi R, Zajicheck A, Kattan M, Fox R. Risk estimates of progressive multifocal leukoencephalopathy related to fingolimod. In: ECTRIMS Online Library. 2018. p. 1775.
61. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med. 2012;367(12):1098–107.
62. Moraes Machado MI, Cunha Matta AP, Apostolos Pereira SL, Alves-Leon SV, Marques VD, Gomes S, et al. Fingolimod prescribed for the treatment of multiple sclerosis in patients younger than age 18 years. Pediatr Neurol. 2015;53(2):166–8.
63. U.S. Food and Drug Administration. Press Announcements - FDA approves new oral drug to treat multiple sclerosis. Office of the Commissioner; [cited 2019 Apr 2]. Available from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm634469.htm.
64. Kappos L, Bar-Or A, Cree BAC, Fox RJ, Giovannoni G, Gold R, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomized, phase 3 study. Lancet. 2018;391(10127):1263–73.
65. Vermersch P, Czlonkowska A, Grimaldi LME, Confavreux C, Comi G, Kappos L, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomized, controlled phase 3 trial. Mult Scler. 2014;20(6):705–16.
66. Chitnis T, Tardieu M, Banwell B, Gücüyener K, Deiva K, Skripchenko N, et al. Evaluation of teriflunomide in children and adolescents with relapsing MS: TERIKIDS phase 3 study design, enrollment update, and baseline data (P4.354). Neurology. 2018;90(15 Supplement):4.354.
67. U.S. Food and Drug Admnistration. Press Announcements - FDA approves new oral treatment for multiple sclerosis. [Cited 2019 Apr 2]; Available from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm634837.htm.
68. Leist TP, Comi G, Cree BAC, Coyle PK, Freedman MS, Hartung HP, et al. Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomized trial. Lancet Neurol. 2014;13(3):257–67.
69. Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Sørensen PS, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):416–26.
70. Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue E-W, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med. 2006;354(9):911–23.
71. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006;354(9):899–910.
72. Miller DH, Soon D, Fernando KT, MacManus DG, Barker GJ, Yousry TA, et al. MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS. Neurology. 2007;68(17):1390–401.
73. Arnal-Garcia C, Garcia-Montero MR, Malaga I, Millan-Pascual J, Oliva-Nacarino P, Ramio-Torrenta L, et al. Natalizumab use in pediatric patients with relapsing-remitting multiple sclerosis. Eur J Paediatr Neurol. 2013;17(1):50–4.
74. Ghezzi A, Pozzilli C, Grimaldi LME, Brescia Morra V, Bortolon F, Capra R, et al. Safety and efficacy of natalizumab in children with multiple sclerosis. Neurology. 2010;75(10):912–7.
75. Kean JM, Rao S, Wang M, Garcea RL. Seroepidemiology of human polyomaviruses. PLoS Pathog. 2009;5(3):e1000363.
76. Huppke P, Hummel H, Ellenberger D, Pfeifenbring S, Stark W, Huppke B, et al. JC virus antibody status in a pediatric multiple sclerosis cohort: prevalence,

conversion rate and influence on disease severity. Mult Scler. 2015;21(4):382–7.
77. Trampe AK, Hemmelmann C, Stroet A, Haghikia A, Hellwig K, Wiendl H, et al. Anti-JC virus antibodies in a large German natalizumab-treated multiple sclerosis cohort. Neurology. 2012;78(22):1736–42.
78. Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med. 2008;358(7):676–88.
79. Naismith RT, Piccio L, Lyons JA, Lauber J, Tutlam NT, Parks BJ, et al. Rituximab add-on therapy for breakthrough relapsing multiple sclerosis: a 52-week phase II trial. Neurology. 2010;74(23):1860–7.
80. Spelman T, Frisell T, Piehl F, Hillert J. Comparative effectiveness of rituximab relative to IFN-beta or glatiramer acetate in relapsing-remitting MS from the Swedish MS registry. Mult Scler. 2018;24(8):1087–95.
81. Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomized controlled phase 3 trial. Lancet. 2012;380(9856):1819–28.
82. Das B, Dimas V, Guleserian K, Lacelle C, Anton K, Moore L, et al. Alemtuzumab (Campath-1H) therapy for refractory rejections in pediatric heart transplant recipients. Pediatr Transplant. 2017;21(1).
83. Kim IK, Choi J, Vo AA, Kang A, Patel M, Toyoda M, et al. Safety and efficacy of alemtuzumab induction in highly sensitized pediatric renal transplant recipients. Transplantation. 2017;101(4):883–9.
84. Kaabak MM, Babenko NN, Samsonov DV, Sandrikov VA, Maschan AA, Zokoev AK. Alemtuzumab induction in pediatric kidney transplantation. Pediatr Transplant. 2013;17(2):168–78.
85. Muraro PA, Douek DC, Packer A, Chung K, Guenaga FJ, Cassiani-Ingoni R, et al. Thymic output generates a new and diverse TCR repertoire after autologous stem cell transplantation in multiple sclerosis patients. J Exp Med. 2005;201(5):805–16.
86. Darlington PJ, Touil T, Doucet J-S, Gaucher D, Zeidan J, Gauchat D, et al. Diminished Th17 (not Th1) responses underlie multiple sclerosis disease abrogation after hematopoietic stem cell transplantation. Ann Neurol. 2013;73(3):341–54.
87. Sormani MP, Muraro PA, Saccardi R, Mancardi G. NEDA status in highly active MS can be more easily obtained with autologous hematopoietic stem cell transplantation than other drugs. Mult Scler. 2017;23(2):201–4.
88.• Burman J, Kirgizov K, Carlson K, Badoglio M, Mancardi GL, De Luca G, et al. Autologous hematopoietic stem cell transplantation for pediatric multiple sclerosis: a registry-based study of the Autoimmune Diseases Working Party (ADWP) and Pediatric Diseases Working Party (PDWP) of the European Society for Blood and Marrow Transplant. Bone Marrow Transplant. 2017;52(8):1133–.
The only trial of hematopoetic stem cell transplantation in children with MS.
89. Freedman MS, Bar-Or A, Atkins HL, Karussis D, Frassoni F, Lazarus H, et al. The therapeutic potential of mesenchymal stem cell transplantation as a treatment for multiple sclerosis: consensus report of the International MSCT Study Group. Mult Scler. 2010;16(4):503–10.
90. Scolding NJ, Pasquini M, Reingold SC, Cohen JA. Cell-based therapeutic strategies for multiple sclerosis. Brain. 2017;140(11):2776–96.
91. Tur C, Moccia M, Barkhof F, Chataway J, Sastre-Garriga J, Thompson AJ, et al. Assessing treatment outcomes in multiple sclerosis trials and in the clinical setting. Nat Rev Neurol. 2018:3–5.
92. Rotstein DL, Healy BC, Malik MT, Chitnis T, Weiner HL. Evaluation of no evidence of disease activity in a 7-year longitudinal multiple sclerosis cohort. JAMA Neurol. 2015;72(2):152–8.
93. Kurtzke JF. Disability rating scales in multiple sclerosis. Ann N Y Acad Sci. 1983;436(1):347–60.
94. Whitaker JN, McFarland HF, Rudge P, Reingold SC. Outcomes assessment in multiple sclerosis trials. Mult Scler. 1995;1(1):37–47.
95. Noseworthy JH, Vandervoort MK, Wong CJ, Ebers GC. Interrater variability with the Expanded Disability Status Scale (EDSS) and Functional Systems (FS) in a multiple sclerosis clinical trial. The Canadian Cooperation MS Study Group. Neurology. 1990;40(6):971–5.
96.•• Waldman AT, Chahin S, Lavery AM, Liu G, Banwell BL, Liu GT, et al. Binocular low-contrast letter acuity and the symbol digit modalities test improve the ability of the Multiple Sclerosis Functional Composite to predict disease in pediatric multiple sclerosis. Mult Scler Relat Disord. 2016;10(2016):73–.
Important paper on the development of clinical outcome measures in pediatric multiple sclerosis.
97. Fischer JS, Rudick RA, Cutter GR, Reingold SC. The Multiple Sclerosis Functional Composite measure (MSFC): an integrated approach to MS clinical outcome assessment. Mult Scler J. 1999;5(4):244–50.
98. Benedict RHB, Deluca J, Phillips G, Larocca N, Hudson LD. Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. Mult Scler J. 2017;23(5):721–33.
99. Novakova L, Zetterberg H, Sundstrom P, Axelsson M, Khademi M, Gunnarsson M, et al. Monitoring disease activity in multiple sclerosis using serum neurofilament light protein. Neurology. 2017;89(22):2230–7.
100.•• van der Vuurst de Vries RM, Wong YYM, Mescheriakova JY, van Pelt ED, Runia TF, Jafari N, et al. High neurofilament levels are associated with clinically definite multiple sclerosis in children and adults with clinically isolated syndrome. Mult Scler J. 2018;1–10.
Diagnostic value of NfL in children with an isolated demyelinating event.
101. Mar S, Piccio L. CSF Neurofilament light chain levels as a biomarker for pediatric demyelinating diseases

(P5.349). Neurology. 2016;86(16 Supplement):5.349.
102. Reinert M, Barro C, Michalak Z, Bruck W, Huppke P, Kropshofer H, et al. Neurofilament light chain is a useful biomarker in paediatric multiple sclerosis. ECTRIMS online library 2018. p. 666.
103. Lambe J, Murphy OC, Saidha S. Can optical coherence tomography be used to guide treatment decisions in adult or pediatric multiple sclerosis? Curr Treat Options Neurol. 2018;20(4).
104. Graves JS, Chohan H, Cedars B, Arnow S, Yiu H, Waubant E, et al. Sex differences and subclinical retinal injury in pediatric-onset MS. Mult Scler. 2017;23(3):447–55.
105. Huhn K, Lammer R, Oberwahrenbrock T, Lammer A, Waschbisch A, Gosar D, et al. Optical coherence tomography in patients with a history of juvenile multiple sclerosis reveals early retinal damage. Eur J Neurol. 2015;22(1):86–92.
106. Sadaka Y, Verhey LH, Shroff MM, Branson HM, Arnold DL, Narayanan S, et al. 2010 McDonald criteria for diagnosing pediatric multiple sclerosis. Ann Neurol. 2012;72(2):211–23.
107. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162–73.
108. Krupp LB, Tardieu M, Amato MP, Banwell B, Chitnis T, Dale RC, 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 J. 2013;19(10):1261–7.
109. Maggi P, Absinta M, Grammatico M, Vuolo L, Emmi G, Carlucci G, et al. Central vein sign differentiates multiple sclerosis from central nervous system inflammatory vasculopathies. Ann Neurol. 2018;83(2):283–94.
110. Sinnecker T, Wuerfel E, Cerda Fuertes N, Meier D, Derfuss T, Gartner J, et al. The central vein sign in paediatric-onset multiple sclerosis. ECTRIMS online library 2018. P.346.
111. Sati P, Oh J, Todd Constable R, Evangelou N, Guttmann CRG, Henry RG, et al. The central vein sign and its clinical evaluation for the diagnosis of multiple sclerosis: a consensus statement from the North American Imaging in Multiple Sclerosis Cooperative. Nat Rev Neurol. 2016;12(12):714–22.
112. Young NP, Weinshenker BG, Parisi JE, Scheithauer B, Giannini C, Roemer SF, et al. Perivenous demyelination: association with clinically defined acute disseminated encephalomyelitis and comparison with pathologically confirmed multiple sclerosis. Brain. 2010;133(Pt 2):333–48.
113. Thannhauser JE, Mah JK, Metz LM. Adherence of adolescents to multiple sclerosis disease-modifying therapy. Pediatr Neurol. 2009;41(2):119–23.
114. Tremlett H, Van der Mei I, Pittas F, Blizzard L, Paley G, Dwyer T, et al. Adherence to the immunomodulatory drugs for multiple sclerosis: contrasting factors affect stopping drug and missing doses. Pharmacoepidemiol Drug Saf. 2008;17(6):565–76.
115. McKay KA, Tremlett H, Patten SB, Fisk JD, Evans C, Fiest K, et al. Determinants of non-adherence to disease-modifying therapies in multiple sclerosis: a cross-Canada prospective study. Mult Scler. 2017;23(4):588–96.
116. Lulu S, Julian L, Shapiro E, Hudson K, Waubant E. Treatment adherence and transitioning youth in pediatric multiple sclerosis. Mult Scler Relat Disord. 2014;3(6):689–95.
117. Schwartz CE, Grover SA, Powell VE, Noguera A, Mah JK, Mar S, et al. Risk factors for non-adherence to disease-modifying therapy in pediatric multiple sclerosis. Mult Scler J. 2018;24(2):175–85.
118. Yeh EA, Grover SA, Powell VE, Alper G, Banwell BL, Edwards K, et al. Impact of an electronic monitoring device and behavioral feedback on adherence to multiple sclerosis therapies in youth: results of a randomized trial. Qual Life Res. 2017;26(9):2333–49.

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