

Treatment Updates in Paediatric-onset Multiple Sclerosis

Aaron W Abrams,^{1,2} Amanda March,¹ Daphne Porat,¹ Kriti Bhayana¹ and Mary Rensel²

1. Center for Pediatric Neurosciences, Cleveland Clinic Foundation, Cleveland, OH, USA; 2. Mellen Center for Multiple Sclerosis, Cleveland Clinic Foundation, Cleveland, OH, USA

DOI: <https://doi.org/10.17925/USN.2022.18.1.42>

A number of new disease-modifying therapies have recently been developed and approved for use in adult-onset multiple sclerosis. However, few treatment options are approved for patients with paediatric-onset multiple sclerosis. There are an increasing number of clinical trials evaluating the efficacy and safety of disease-modifying therapies in children and teens living with multiple sclerosis. Clinical trials are difficult to complete in rare diseases like paediatric-onset multiple sclerosis; however, it is critical to assess safety and monitoring in this vulnerable population by applying robust research methodology to randomized controlled clinical trials. Longer-term extension analyses are also needed to better evaluate the efficacy, dosing and long-term safety of adult disease-modifying therapy for use in paediatric-onset multiple sclerosis. Future research should focus on defining optimal first-line disease-modifying therapy in paediatric-onset multiple sclerosis as related to both efficacy and safety, improving recruitment and completion rates of clinical trials, identifying relevant biomarkers of disease activity, analysing outcome measures related to treatment response and assessing long-term safety for this unique population living with a chronic disease.

Keywords

Pediatrics, multiple sclerosis, disease-modifying therapy, neuroimmunology, clinical trial

Disclosures: Aaron W Abrams, Amanda March, Daphne Porat and Kriti Bhayana have no financial or non-financial relationships or activities to declare in relation to this article. Mary Rensel has received research funding from PPD, Roche, Genentech, Novartis, Biogen, Genentech, CBJ Foundation and NMSS and patient education funds from Genzyme and CBJ Foundation. She has served on the Data Safety Monitoring Committee for Biogen and has been a speaker/consultant for Serono, Novartis, Genentech, Genzyme, Horizon, TG, Improve Consulting, Kijia and MSAA. She is founder of Brain Fresh and has a joint venture called Brain Ops Group.

Review process: Double-blind peer review.

Compliance with ethics: This study involves a review of the literature and did not involve any studies with human or animal subjects performed by any of the authors.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Authorship: The named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Access: This article is freely accessible at touchNEUROLOGY.com. © Touch Medical Media 2022

Received: 16 March 2022

Accepted: 4 May 2022

Published online: 22 June 2022

Citation: *touchREVIEWS in Neurology*. 2022;18(1):42–8

Corresponding author: Aaron W Abrams, MD, Center for Pediatric Neurosciences and Mellen Center for Multiple Sclerosis, Cleveland Clinic, Cleveland, OH 44195, USA. E: abramsa@ccf.org

Support: No funding was received for the publication of this article.

Paediatric-onset multiple sclerosis (POMS) is the symptom onset and diagnosis of multiple sclerosis (MS) before the age of 18.¹ Diagnostic criteria were revised by the International Pediatric MS Study Group in 2013. Compared to patients with adult-onset MS (AOMS), young patients are less likely to develop primary or secondary progressive MS and more likely to follow a relapsing–remitting course. Although early relapses in patients with POMS tend to be more highly inflammatory and more frequent,² children seem to demonstrate more resiliency, recovering more quickly and effectively from each attack. However, there is growing evidence that patients with POMS still require early treatment with a highly effective disease-modifying therapy (DMT) to help prevent significant long-term disability.^{3,4} Over the past decade, there has been a rapid development of new DMTs for AOMS, including four that have been newly US Food and Drug Administration (FDA)-approved in the past 2 years (*Table 1*).^{5–8} These include ofatumumab and several new S1P receptor modulators (*Table 1*). Ofatumumab is a B-cell depleting therapy similar to rituximab and ocrelizumab but is given by monthly subcutaneous injection following an induction of three weekly injections.⁵ After observation of the first dose to ensure safety, patients can then dose themselves at home without the need to travel to an infusion centre. The new S1P modulators were developed as alternatives to fingolimod, with the goal of improved safety such as a lack of stringent first-dose cardiac monitoring with some of the new products.⁹ However, the short- and long-term safety, dosing and effectiveness of most AOMS DMTs in the POMS population requires further clarification. New clinical trials exploring DMT use in POMS continue to emerge.

From 2006 through 2020, a total of three treatment trials analysing DMT use in POMS have been published. These include interferon β -1a, fingolimod and teriflunomide.^{10–12} Interferon β -1a is a first-generation injectable interferon requiring frequent dosing, fingolimod is a once-a-day oral sphingosine 1-phosphate (S1P) receptor modulator and teriflunomide is a once-a-day oral pyrimidine synthesis inhibitor.

The first treatment trial examined interferon β -1a use in 16 children with POMS, demonstrating overall stable median Expanded Disability Status Score and magnetic resonance imaging (MRI) activity in three patients, with worsening in six patients. It was well-tolerated, with side effects including flu-like symptoms, isolated myalgias and injection-site reactions. Treatment was not interrupted in any cases due to adverse events.¹⁰ Compared with interferon β -1a, the fingolimod trial demonstrated a relative decrease of 88% in adjusted annualized relapse rate, 53% reduction in annualized rate of new or newly enlarged T2 lesions and a higher rate of serious adverse events.¹¹ A 2-year follow-up analysis showed sustained reduction in MRI activity and annualized rate of brain atrophy,¹³ continued control of disease activity and less disability progression.¹⁴ The third treatment trial compared teriflunomide against placebo in 166 patients with POMS,

Table 1: Approved adult-onset multiple sclerosis therapies from 2020 to present⁵⁻⁸

Drug	Brand name, approval year	Mechanism of action	Maintenance dosing
INJECTABLES			
Ofatumumab	Kesimpta™, 2020 ⁵	Monoclonal antibody directed against the CD20 antigen on the surface of B lymphocytes, causing temporary depletion of B cells	20 mg subcutaneously monthly
ORALS			
Ozanimod	Zeposia™, 2020 ⁶	Decreases CNS inflammation by blocking entry of activated T cells from lymph nodes to blood stream	0.92 mg po daily
Ponesimod	Ponvory™, 2021 ⁷	Decreases CNS inflammation by blocking entry of activated T cells from lymph nodes to blood stream	20 mg po daily
Monomethyl Fumarate	Bafiertam™, 2020 ⁸	May decrease inflammation by improving cellular response to oxidative stress by activating nuclear factor-like 2 pathway	190 mg po bid

bid = twice daily; CNS = central nervous system; po = by mouth.

demonstrating no significant difference in time to first confirmed clinical relapse between groups, and a reduction in MRI lesions in the teriflunomide group compared with placebo.¹² The safety profile was similar as that observed in adult patients, although there was a higher rate of pancreatitis with teriflunomide in paediatric patients compared to adults. This has only been reported in adult patients post-marketing.^{12,15}

Most POMS DMT data comes from two retrospective analysis papers published in 2018 and 2020.^{16,17} For both analyses, clinical data was collected prospectively from a network of 12 Pediatric MS Centers throughout the USA and Canada. The 2020 retrospective paper looked at a total of 741 paediatric patients with MS and clinically isolated syndrome between 2011 and 2019 using propensity scores.¹⁷ The most significant finding was that early initiation of a highly effective DMT (as defined in the adult literature) led to more favourable outcomes compared to injectables.¹⁸ Furthermore, the DMT safety profiles were overall similar to those observed in adult trials.^{16,17}

The purpose of this review is to provide updates on the most recent research investigating DMT use in POMS.

Methods

This narrative review includes a study of both publications and clinical trials published after 2020. For recent POMS DMT trials, a search was conducted using ClinicalTrials.gov by entering “pediatric multiple sclerosis” under [Condition or disease]. The following filters were subsequently checked under [Recruitment Status]: “recruiting”, “active not recruiting” and “completed”. To restrict the results to only recent trials, all “completed” studies prior to 2020 were excluded. All “active” studies, even those prior to 2020, were included, as some of the follow-up analyses have not yet been completed. Additional filters applied included “child (birth-17)” for [age] and “interventional” for [study type]. To restrict the results to include only drug treatment trials, only those listing the name of a specific MS DMT listed under the “intervention” column were included.

For recent publications, a search was conducted using PubMed by entering the following keywords under [Title/Abstract]: “pediatric multiple sclerosis” and the names of all available MS DMTs. To restrict the results to include only the most recent articles, date range filters were set to between “2020/01/01” and “2021/12/31”. All article types were subsequently included in the results.

Results

The POMS clinical treatment trials search yielded nine investigations (Table 2)¹⁹⁻²⁷ and the publications search yielded 10 publications (Table 3).^{12,13,28-35} Of the nine new clinical treatment trials, there were four phase III investigations initiated after 2019 (Table 2). The first, comparing dimethyl fumarate (DMF) with peginterferon β -1a, aims to show that DMF is effective and safe enough to warrant its use as a first-line therapy over first-generation injectables (Study to evaluate the efficacy and safety of dimethyl fumarate [Tecfidera] and peginterferon beta-1a [Plegridy] for the treatment of relapsing-remitting multiple sclerosis in pediatric participants; ClinicalTrials.gov identifier: NCT03870763).²⁷ The second, comparing ocrelizumab with fingolimod, was likely designed for two major reasons: to demonstrate that ocrelizumab is at least as effective as fingolimod and therefore warrants FDA approval in POMS, and to investigate whether ocrelizumab is more effective than fingolimod and thus should serve as the preferred first-line option for patients with POMS (A study to evaluate safety and efficacy of ocrelizumab in comparison with fingolimod in children and adolescents with relapsing-remitting multiple sclerosis [Operetta 2]; ClinicalTrials.gov identifier: NCT05123703).²⁴ The third trial, which compares ofatumumab and siponimod to fingolimod, also likely aims to clarify the optimal first-line DMT in POMS (Efficacy and safety of ofatumumab and siponimod compared to fingolimod in pediatric patients with multiple sclerosis [NEOS]; ClinicalTrials.gov identifier: NCT04926818).²³ Siponimod is a newer once-a-day oral S1P modulator alternative to fingolimod.⁹ The fourth trial compares peginterferon β -1a with the active comparator interferon β -1a to evaluate its effectiveness and safety in POMS (A study to evaluate the safety, tolerability, and efficacy of BIIB017 [peginterferon beta-1a] in pediatric participants for the treatment of relapsing-remitting multiple sclerosis; ClinicalTrials.gov identifier: NCT03958877).²¹

Our comprehensive literature search yielded 10 recent manuscripts on DMT use in POMS, of which there were three trial results papers and one review article (Table 3). The remainder were case reports and case series. In the first trial article, Arnold et al. reported on the predefined MRI outcomes from the trial, demonstrating that fingolimod significantly reduced MRI activity and annualized rate of brain atrophy compared to interferon β -1a (Safety and efficacy of fingolimod in pediatric patients with multiple sclerosis [PARADIGMS]; ClinicalTrials.gov identifier: NCT01892722).^{13,20} In the second, Alroughani et al. published the results of a 96-week extension to the phase II DMF trial for patients 13 to 17 years of age with relapsing-

Table 2: Paediatric-onset multiple sclerosis treatment investigations¹⁹⁻²⁷

Study, NCT identifier	Recruitment status	Year	Enrollment	Study phase	Study design	Primary objective	Secondary objectives
Efficacy, safety and pharmacokinetics of teriflunomide in pediatric patients with relapsing forms of MS (TERIKIDS) (NCT02201108) ¹⁹	Completed	2014–2021	Actual: 166	Phase III	Teriflunomide in randomized, placebo-controlled, followed by open-label extension period; Parallel assignment; Quadruple blinding	Time to first relapse	Safety and tolerability; Pharmacokinetics; Effect on disease progression
Safety and efficacy of fingolimod in pediatric patients with MS (NCT01892722) ²⁰	Recruiting (Extension Phase)	2013–2028	Goal: 220	Phase III	Fingolimod in open-label extension phase	Frequency of relapses in patients treated for up to 24 months	Pharmacokinetics; Time to first relapse; Effect on MRI
Evaluate the safety, tolerability, and efficacy of peginterferon β -1a in pediatric patients with RRMS (NCT03958877) ²¹	Recruiting	2019–2029	Goal: 142	Phase III	Peginterferon β -1a in randomized, active control to interferon β -1a, followed by open-label extension period; Parallel assignment; Open label	ARR at Week 96 Percentage of participants with AEs, serious AEs, and AEs leading to study treatment discontinuation	Safety, tolerability and descriptive efficacy; Pharmacokinetics; Long-term safety (open-label extension)
Safety, tolerability, pharmacokinetics and pharmacodynamic effects of ocrelizumab in pediatric patients with RRMS (NCT04075266) ²²	Recruiting	2020–2027	Goal: 36	Phase II	Ocrelizumab in parallel assignment; Open label	Serum concentration of ocrelizumab, Levels of CD19+ B-cell count in blood	AEs; Level of circulating WBCs; Effect on certain developmental milestones including height, growth velocity and Tanner staging; ADAs; Antibody titers against vaccines; Non-MS CNS pathology on Brain MRI; Serum immunoglobulins
Efficacy and safety of ofatumumab and siponimod compared with fingolimod in pediatric patients with MS (NEOS) (NCT04926818) ²³	Recruiting	2021–2029	Goal: 180	Phase III	Ofatumumab in randomized, active control to interferon β -1a, followed by open-label extension period; Parallel assignment; Open label	ARR	ARR as compared with interferon- β 1a; Annualized T2 lesion rate; Pharmacokinetics of ofatumumab and Siponimod; Percentage of participants with ADAs; AEs or serious AEs (extension phase)
Safety and efficacy of ocrelizumab in comparison with fingolimod in pediatric patients with RRMS (Operetta 2) (NCT05123703) ²⁴	Recruiting	2022–2025	Goal: 233	Phase III	Ocrelizumab in randomized double-dummy to fingolimod; Parallel assignment; Quadruple blinding	ARR	AEs; Effect on disease progression on MRI; ADAs at baseline and during study

Table 2: Continued

Study, NCT identifier	Recruitment status	Year	Enrollment	Study phase	Study design	Primary objective	Secondary objectives
Efficacy and safety of BG00012 in pediatric patients with RRMS (CONNECT) (NCT02283853) ²⁵	Active, not recruiting	2014–2025	Actual: 156	Phase III	Dimethyl fumarate in randomized, active control to interferon beta type 1a, followed by open-label extension period; Parallel assignment; Open label	Patients without new/newly enlarging T2 hyperintense lesions on MRI at Week 96; AEs, serious AEs and discontinuation due to AEs (extension phase)	Number of new/newly enlarging T2 hyperintense lesions at weeks 24 and 96; Proportion of patients free of new/newly enlarging T hyperintense lesions at weeks 24 and 48; Proportion of patients free of new Brain MRI activity at weeks 24, 48 and 96; Time to first relapse; Proportion of patients who experience no relapse; ARR; AEs, serious AEs, and discontinuation due to AEs up to week 96; QoL measures (fatigue, Peds QL, EDSS); Vital signs, electrocardiograms and monitoring clinical laboratory data
Evaluate the efficacy, safety and tolerability of alemtuzumab in pediatric patients with RRMS with disease activity on prior DMT (LemKids) (NCT03368664) ²⁶	Active, not recruiting	2017–2025	Goal: 50	Phase III	Alemtuzumab in single-group assignment; Open label	Number of new or enlarging T2 lesions	Change in EDSS; ARR; Assessment of cognition test scores; Paediatric QoL measures; Pharmacokinetics; Pharmacodynamics; ADA formation; AEs
Evaluate the efficacy and safety of dimethyl fumarate and peginterferon β -1a for the treatment of RRMS in pediatric patients (NCT03870763) ²⁷	Active, not recruiting	2019–2021	Actual: 11	Phase III	Dimethyl fumarate in randomized, placebo-controlled; Parallel assignment; Quadruple blinding	Time to first relapse	ARR; AEs or serious AEs; Effect on MRI

ADA = anti-drug antibody; AE = adverse event; ARR = annualized relapse rate; CNS = central nervous system; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale, IV = intravenous; MS = multiple sclerosis; MRI = magnetic resonance imaging; QoL = quality of life; RRMS = relapsing–remitting multiple sclerosis; WBC = white blood cell.

remitting multiple sclerosis (RRMS) (Efficacy and safety of BG00012 in pediatric patients with RRMS [CONNECT]; ClinicalTrials.gov identifier: NCT02283853, Extension study of BG00012 in pediatric subjects with relapsing remitting multiple sclerosis [FOCUS]; ClinicalTrials.gov identifier: NCT02555215).^{25,28,36,37} DMF is a twice daily oral activator of the nuclear factor (erythroid-derived 2)-like pathway.³⁸ Of the patients with POMS enrolled, the authors found similar long-term safety and efficacy to that observed in the AOMS trials.^{28,39} Therefore, they concluded that patients with POMS might similarly benefit from treatment with DMF.²⁸ In the paper by Chitnis et al., the results of the first randomized, double-blind, placebo-controlled, phase III trial of teriflunomide for patients with POMS were published (Efficacy, safety and pharmacokinetics of teriflunomide in pediatric patients with relapsing forms of multiple sclerosis [TERIKIDS]; ClinicalTrials.gov identifier: NCT02201108).^{12,19} After 96 weeks, there was no significant difference in time to first relapse compared to placebo. Of note, the transition from double-blind to open-label treatment occurred earlier and more frequently than originally anticipated, with 37 of the original 57 patients assigned to placebo completing the double-blind treatment period early due to either high MRI activity or

confirmed relapses. The authors felt this decreased the study's power and may have skewed the results against treatment efficacy. The results did demonstrate radiologic improvement in patients treated with teriflunomide, with a reduced number of new or enlarging T2 and gadolinium-enhancing T1 lesions compared to placebo. Teriflunomide was also well-tolerated with no new safety concerns as compared to adults.¹² Based on these findings, teriflunomide was approved for treatment of patients with POMS ages 10 or older in the European Union in June 2021.⁴⁰ The FDA, however, did not deem this data sufficient enough to justify its approval for POMS in the USA, highlighting the need for more clinical trial data.

Our search yielded one review paper, which was published in October 2021 by Ghezzi et al.³⁵ The authors examined rituximab use in POMS and related disorders in the hopes of establishing a more standardized protocol.³⁵ The authors began by mentioning the phase I study of ocrelizumab, which is now transitioning into phase III (Table 2). They then summarized rituximab use in AOMS and presented the available retrospective data published on rituximab use in several paediatric

Table 3: Paediatric-onset multiple sclerosis therapy publications from 2020 to the present^{12,13,28–35}

Title	Year	Type	Treatment	Participants	Conclusions
Effect of fingolimod on MRI outcomes in patients with paediatric-onset MS: results from the phase III PARADIGMS study ¹³	2020	Phase III clinical trial	Fingolimod	215	Fingolimod significantly reduced MRI activity and annualized rate of brain atrophy for up to 2 years versus interferon β -1a in paediatric-onset MS
Delayed-release dimethyl fumarate safety and efficacy in paediatric patients with RRMS ²⁸	2021	Phase II clinical trial	Dimethyl fumarate	17	Long-term safety profile in paediatric patients seems consistent with that seen in adults
Safety and efficacy of teriflunomide in pediatric-onset MS (TERIKIDS): a multicentre, double-blind, phase III, randomized, placebo-controlled trial ¹²	2021	Phase III clinical trial	Teriflunomide	166	No significant difference in time to first relapse compared to placebo, reduced number of new T2 lesions. No new or unexpected safety concerns
Short-term outcomes of pediatric-onset MS patients treated with alemtuzumab at a Canadian University multiple sclerosis clinic ²⁹	2020	Case report	Alemtuzumab	2	2 patients with paediatric-onset MS experienced improvement in EDSS with alemtuzumab without serious infusion reactions, infections or definite relapses
Fingolimod in paediatric MS: three case reports ³⁰	2021	Case report	Fingolimod	3	Fingolimod as first- or second-choice therapy was well-tolerated, with radiologic stability in 3 patients over a range of 11–17 months of treatment
Two-year follow-up during fingolimod treatment in a pediatric-onset MS patient still active on first-line treatment ³¹	2021	Case report	Fingolimod	1	Treatment with fingolimod was effective following treatment with interferon β -1a
Efficacy of fingolimod after switching from interferon β -1a in an adolescent with MS: case report ³²	2021	Case report	Fingolimod	1	Fingolimod was well-tolerated in patients with paediatric-onset MS following interferon β -1a, with clinical and radiologic stability after 2 years
Fingolimod as a first- or second-line treatment in a mini-series of young Hellenic patients with adolescent-onset MS: focus on immunological data ³³	2021	Case report	Fingolimod	7	The response of fingolimod in paediatric-onset MS seems to be partially dependent on age and previous immunomodulatory therapy
Effective therapy in highly active pediatric-onset multiple sclerosis ³⁴	2021	Case Report	Natalizumab	3	Natalizumab was effective and well-tolerated in paediatric RRMS patients
Rituximab in patients with pediatric-onset MS and other demyelinating disorders of the CNS: Practical considerations ³⁵	2021	Review	Rituximab	Not applicable	Additional studies are needed to aid in standardization of rituximab as possible DMT for patients with paediatric-onset MS

CNS = central nervous system; DMT = disease-modifying treatment; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; MS = multiple sclerosis; RRMS = relapsing–remitting multiple sclerosis.

neuroinflammatory diseases.⁴¹ The 2013 International Pediatric MS Study Group's position on rituximab is that it has significant potential benefit but requires further investigation to establish a standardized therapeutic protocol.⁴² The review authors go on to propose a practical framework for rituximab use in POMS, giving particular attention to dosing, frequency and monitoring parameters. At present, rituximab has not been formally approved for use in POMS by the FDA or the Canadian Health Products and Food Branch. Of note, it has also not been FDA-approved for AOMS. Therefore, the authors emphasized the need for additional short- and long-term data on rituximab use in POMS.³⁵ They also raised specific concerns surrounding the increased infection risks in light of the coronavirus disease 2019 (COVID-19) pandemic.³⁵

Our search yielded a number of new case studies. In a case series of three patients, Merô et al. explained how poor outcomes observed in almost 45% of patients with POMS taking first-generation injectables prompted the PARADIGMS and CONNECT trials to examine higher-efficacy options more closely.³⁴ They then presented three active patients with RRMS successfully treated with natalizumab.³⁵ A paper by Hunt and Traboulsee described two patients with POMS treated with alemtuzumab with favourable responses.²⁹ Multiple additional case reports supported the results of the PARADIGMS trial, showing that fingolimod was well-

tolerated and effective as first- or second-line therapy in POMS.^{30–33} This included a report of three patients by Ferilli et al. with radiologic disease stability 11–17 months after initiation of fingolimod.³⁰ Furthermore, two separate case reports by Immovilli et al. and Amidei et al. each presented a patient with POMS who switched to fingolimod following failed interferon β -1a therapy, resulting in disease stability.^{31,32} Finally, a case report by Gontika et al. described seven patients, three of whom were treatment-naïve and received fingolimod.³³ Their level of disease activity following treatment suggested that response to fingolimod may be at least partially dependent on age and prior DMT, with younger and treatment-naïve patients having potentially worse outcomes.³³

Discussion

Based on our above comprehensive review of the literature, the most recent research provides growing support for starting patients newly diagnosed with POMS on highly effective DMTs as early as possible. The initiation of four new clinical POMS DMT trials will hopefully provide further justification for this. The results may also help facilitate payor approvals and instill providers with more confidence to prescribe newer DMTs to patients with POMS. One unanswered question is the use of newer DMTs in patients less than 10 years of age. Since this cohort represents such a small fraction of the overall MS population, post-hoc

Table 4: International paediatric multiple sclerosis study group recommendations for clinical trials in paediatric-onset multiple sclerosis⁴⁷

Regulatory recommendations	Trial design recommendations	Safety monitoring recommendations
Different world regions' regulatory agencies should harmonize clinical trial design requirements for paediatric MS therapeutic trials of immunomodulating agents	Placebo-controlled trials of immunomodulatory agents proven effective in adult patients with MS are inappropriate in paediatric patients with MS	Open-label extension studies should be mandated for all clinical trials in paediatric-onset MS populations
No more than one phase III clinical trial should be performed for the same pharmacologic agent	Future phase III registration trials in adults should consider enrolment of teenager patients with MS	Open-label studies or registries should be designed to monitor safety in patients ages 12 and under
<i>In vitro</i> and animal studies related to the use of a drug in paediatric patients should be performed early on to avoid postponing appropriate testing in human paediatric patients	Open-label study, including PK/PD and safety endpoints, should be considered as sufficient for registration in paediatric-onset MS for agents that have been well-studied in adults and have demonstrated through PD and statistical modelling extrapolated predictions for the paediatric age range that would support efficacy	
PK and PD paediatric studies should be completed for all new agents to allow identification of appropriate paediatric dosing	A short, controlled trial with an MRI primary endpoint is recommended rather than a clinical endpoint in the case that an open-label study (including PK, PD and safety endpoints) is deemed insufficient for registration in paediatric-onset MS; provided that the pivotal adult study for the same agent demonstrated a strong relationship between clinical efficacy and MRI endpoints In randomized controlled trials of immunomodulating agents, the control drug may be fingolimod, or other agents commonly used in paediatric-onset MS For agents for which a phase III trial with a clinical primary endpoint is mandated by regulatory agencies, time to event analyses should be favoured over ARR as this allows for prompter switch to more effective therapies For add-on trials, the new agent could be compared to placebo, provided that immunomodulatory therapies are maintained	

ARR = annualized relapse rate; MRI = magnetic resonance imaging; MS = multiple sclerosis; PD = pharmacodynamics; PK = pharmacokinetics.

analyses often lack sufficient power and introduce additional biases. Moreover, this particularly vulnerable population presents additional ethical challenges, and a lack of standardized weight-based dosing guidelines makes prescribing newer DMTs to such patients challenging for providers. There are on-going trials looking at the pharmacodynamics of DMT use based on various weights and ages in POMS.^{22,26} It is also important to learn from other subspecialties in this regard, as rituximab is often the only medication considered in very young patients with POMS, with dosing regimens largely based on experience with paediatric rheumatological disorders.⁴¹

Recent legislation in both the USA and Europe has mandated a good faith effort for pharmaceutical companies to complete POMS trials.⁴² Clinical trials in POMS are difficult to complete for a number of reasons, including patient recruitment and the rarity of the disease. For example, only 166 patients with POMS were enrolled in the TERIKIDS trial over a 5-year period at 57 different centres across 22 countries, in comparison to its adult trial counterpart, which enrolled 1088 patients over 4 years at 127 different sites across 21 countries.^{11,43} As discussed in a commentary by Sormani and Waubant, the statistical significance for the primary endpoint of the TERIKIDS trials was not reached despite the same effect being observed in adult teriflunomide trials for reduction in new MRI lesions and ARR. This was likely a result of the study being underpowered due to small trial size.⁴⁴ Nonetheless, the European Union deemed the results worthy enough to approve teriflunomide for use in POMS. The FDA, however, did not. Unless new strategies are applied to paediatric drug trials, underpowered studies

will likely continue to hinder efforts to gain FDA approval of new DMTs to treat POMS.

Other research barriers include the global COVID-19 pandemic, lack of consensus regarding primary outcome and quality of life measures, and ethical concerns. Additional POMS trials are necessary to evaluate the pharmacokinetics, safety and efficacy required to gain regulatory approval and to enhance medication access and long-term outcomes for patients with POMS. Unique biomarkers of POMS may help to assist in the precision of POMS clinical trials. For example, optical coherence tomography and neurofilament light chain are being evaluated as possible means to clarify the level of disease activity in POMS.^{45,46} A global summit was also held in 2019 to formulate 13 clear mandates to assist in designing, recruiting and completing POMS clinical trials (Table 4).⁴⁷

Conclusions

The number of new highly effective DMT options for adult MS that have emerged over the past decade is impressive. When designing clinical MS trials, there is a general sense that adult trials must always be performed prior to the inclusion of paediatric patients, often due to recruitment, safety and ethical challenges.⁴⁸ This can create significant delays in gaining FDA approval of adult drugs for use in the paediatric population. Fingolimod, for example, was approved for use in AOMS in 2010, but not until 2018 for POMS.⁴⁹ In light of the growing evidence supporting the safety and effectiveness of adult DMTs in paediatric patients, it is worth reconsidering whether the exclusion of paediatric patients from adult research trials remains in the best interest of patients

with POMS. Some adult MS trials included paediatric patients, leading to important findings. For instance, a trial of satralizumab in 2019 included adults and adolescents with neuromyelitis optica spectrum disorders, and adolescents were analysed as part of the whole cohort (Efficacy and safety study of satralizumab (SA237) as add-on therapy to treat participants with neuromyelitis optica [NMO] and NMO Spectrum Disorder [NMOsD]; ClinicalTrials.gov identifier: NCT02028884).⁵⁰ This can avoid the significant delays that often occur in the completion of dedicated paediatric trials, often by several years. Priority should

therefore be placed on incorporating paediatric patients into adult trials to ensure enough power is achieved to yield meaningful results. This is also important for gaining FDA approval for newer DMTs in POMS, so that these medications can become more readily accessible and available for immediate use to help prevent long-term disability. Until such a paradigm shift occurs, the profound advances that continue to be made in the treatment of adult MS will remain under-utilized in patients with POMS, despite growing evidence that children may most benefit from such interventions. □

- Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: Revisions to the 2007 definitions. *Mult Scler*. 2013;19:1261–7.
- Alroughani R, Boyko A. Pediatric multiple sclerosis: A review. *BMC Neurol* 2018;18:27.
- Vollmer BL, Wolf AB, Sillau S, et al. Evolution of disease modifying therapy benefits and risks: An argument for de-escalation as a treatment paradigm for patients with multiple sclerosis. *Front Neurol*. 2022;12:799138.
- Waubant E, Banwell B, Wasmer E, et al. Clinical trials of disease-modifying agents in paediatric MS: Opportunities, challenges, and recommendations from the IPMSSG. *Neurology*. 2019;92:2538–49.
- U.S. Food and Drug Administration. Kesimpta prescribing information. 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/125326s070bl.pdf (accessed 14 May 2022).
- U.S. Food and Drug Administration. Zeposia prescribing information. 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/209899s000bl.pdf (accessed 14 May 2022).
- U.S. Food and Drug Administration. Ponvory prescribing information. 2021. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/213498s000bl.pdf (accessed 14 May 2022).
- U.S. Food and Drug Administration. Bafiertam prescribing information. 2021. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/210296s000bl.pdf (accessed 14 May 2022).
- McGinley MP, Cohen JA. Sphingosine 1-phosphate receptor modulators in multiple sclerosis and other conditions. *Lancet*. 2011;398:1184–94.
- Mikaeloff Y, Moreau T, Debouverie M, et al. Interferon-beta treatment in patients with childhood-onset multiple sclerosis. *J Pediatr*. 2001;139:443–6.
- Chitnis T, Arnold DL, Banwell B, et al. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. *N Engl J Med*. 2018;379:1017–27.
- Chitnis Tanuja C, Banwell B, Kappos L, et al. Safety and efficacy of teriflunomide in paediatric multiple sclerosis (TERIKIDS): A multicentre, double-blind, phase 3, randomised, placebo-controlled trial. *Lancet Neurol*. 2021;20:1001–11.
- Arnold DL, Banwell B, Bar-Or A, et al. Effect of fingolimod on MRI outcomes in patients with paediatric-onset multiple sclerosis: Results from the phase 3 PARADIGM MS study. *J Neurol Neurosurg Psychiatry*. 2020;91:483–92.
- Deiva K, Huppke P, Banwell B, et al. Consistent control of disease activity with fingolimod versus IFN β -1a in paediatric-onset multiple sclerosis: Further insights from PARADIGMS. *J Neurol Neurosurg Psychiatry*. 2020;91:58–66.
- Comi G, Freedman MS, Kappos L, et al. Pooled safety and tolerability data from four placebo-controlled teriflunomide studies and extensions. *Mult Scler Relat Disord*. 2016;5:97–104.
- Krysko KM, Graves JS, Rensel M, et al. Use of newer disease-modifying therapies in pediatric multiple sclerosis in the US. *Neurology*. 2018;91:1778–87.
- Krysko KM, Graves JS, Rensel M, et al. Real-world effectiveness of initial disease-modifying therapies in pediatric multiple sclerosis. *Ann Neurol*. 2020;88:42–55.
- Brown JW, Coles A, Horakova D, et al. Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis. *JAMA*. 2019;321:175–87.
- ClinicalTrials.gov. Efficacy, safety and pharmacokinetics of teriflunomide in pediatric patients with relapsing forms of MS (TERIKIDS). ClinicalTrials.gov Identifier: NCT02201108. Available at: <https://clinicaltrials.gov/ct2/show/NCT02201108> (accessed 24 January 2022).
- ClinicalTrials.gov. Safety and efficacy of fingolimod in pediatric patients with multiple sclerosis. ClinicalTrials.gov Identifier: NCT01892722. Available at: <https://clinicaltrials.gov/ct2/show/NCT01892722> (accessed 24 January 2022).
- ClinicalTrials.gov. A study to evaluate the safety, tolerability, and efficacy of BIB017 (peginterferon beta-1a) in pediatric participants for the treatment of relapsing-remitting multiple sclerosis. ClinicalTrials.gov Identifier: NCT03958877. Available at: <https://clinicaltrials.gov/ct2/show/NCT03958877> (accessed 24 January 2022).
- ClinicalTrials.gov. A study of ocrelizumab in children and adolescents with relapsing-remitting multiple sclerosis. ClinicalTrials.gov Identifier: NCT04075266. Available at: <https://clinicaltrials.gov/ct2/show/NCT04075266> (accessed 24 January 2022).
- ClinicalTrials.gov. Efficacy and safety of fatumumab and siponimod compared to fingolimod in pediatric patients with multiple sclerosis (NEOS). ClinicalTrials.gov Identifier: NCT04926818. Available at: <https://clinicaltrials.gov/ct2/show/NCT04926818> (accessed 24 January 2022).
- ClinicalTrials.gov. A study to evaluate safety and efficacy of ocrelizumab in comparison with fingolimod in children and adolescents with relapsing-remitting multiple sclerosis (Operetta 2). ClinicalTrials.gov Identifier: NCT05123703. Available at: <https://clinicaltrials.gov/ct2/show/NCT05123703> (accessed 24 January 2022).
- ClinicalTrials.gov. Phase 3 efficacy and safety study of BG00012 in pediatric subjects with relapsing-remitting multiple sclerosis (CONNECT). ClinicalTrials.gov Identifier: NCT02283853. Available at: <https://clinicaltrials.gov/ct2/show/NCT02283853> (accessed 24 January 2022).
- ClinicalTrials.gov. A study to evaluate efficacy, safety, and tolerability of alemtuzumab in pediatric patients with RMS with disease activity on prior DMT (LemKIDS). ClinicalTrials.gov Identifier: NCT03368664. Available at: <https://clinicaltrials.gov/ct2/show/NCT03368664> (accessed 24 January 2022).
- ClinicalTrials.gov. Study to evaluate the efficacy and safety of dimethyl fumarate (Tecfidera) and peginterferon beta-1a (Plegridy) for the treatment of relapsing-remitting multiple sclerosis in pediatric participants. ClinicalTrials.gov Identifier: NCT03870763. Available at: <https://clinicaltrials.gov/ct2/show/NCT03870763> (accessed 24 January 2022).
- Alroughani R, Huppke P, Mazurkiewicz-Beldzinska M, et al. Delayed-release dimethyl fumarate safety and efficacy in pediatric patients with relapsing-remitting multiple sclerosis. *Front Neurol*. 2021;11:606418.
- Hunt DJ, Traboulee A. Short-term outcomes of pediatric multiple sclerosis patients treated with alemtuzumab at a Canadian University Multiple Sclerosis Clinic. *Mult Scler J Exp Transl Clin*. 2020;6:2055217320926613.
- Ferilli MAN, Papetti L, Valeriani M. Fingolimod in pediatric multiple sclerosis: Three case reports. *Neurol Sci*. 2021;42(Suppl. 1):19–23.
- Immovilli P, Rota E, Morelli N, Guidetti D. Two-year follow-up during fingolimod treatment in a pediatric multiple sclerosis patient still active on first-line treatment. *Neurol Sci*. 2021;42(Suppl. 1):15–8.
- Amidei A, Siciliano G, Pasquali L. Efficacy of fingolimod after switching from interferon β -1a in an adolescent with multiple sclerosis: Case report. *Neurol Sci*. 2021;42(Suppl. 1):5–7.
- Gontika M, Skarlis C, Markoglou N, et al. Fingolimod as a first- or second-line treatment in a mini-series of young hellenic patients with adolescent-onset multiple sclerosis: Focus on immunological data. *Neurol Sci*. 2021;43:2641–9.
- Merò G, Mòser J, Liptai Z, et al. [Effective therapy in highly active pediatric multiple sclerosis]. *Ideggyógyászati Szemle*. 2021;74:413–24.
- Ghezzi A, Banwell B, Bar-Or A, et al. Rituximab in patients with pediatric multiple sclerosis and other demyelinating disorders of the CNS: Practical considerations. *Mult Scler*. 2021;27:1814–22.
- ClinicalTrials.gov. Extension Study of BG00012 in Pediatric Subjects With Relapsing Remitting Multiple Sclerosis. ClinicalTrials.gov Identifier: NCT02555215. Available at <https://clinicaltrials.gov/ct2/show/NCT02555215> (accessed 17 May 2022).
- Alroughani R, Das R, Penner N, et al. Safety and efficacy of delayed-release dimethyl fumarate in pediatric patients with relapsing multiple sclerosis (FOCUS). *Pediatr Neurol*. 2018;83:19–24.
- Olek MJ, Mowry E. Disease-modifying therapies for multiple sclerosis: Pharmacology, administration, and adverse effects. 2022. Available at: www.uptodate.com/contents/disease-modifying-therapies-for-multiple-sclerosis-pharmacology-administration-and-adverse-effects (accessed 16 May 2022).
- Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med*. 2012;367:1098–107.
- Sanofi press release. European Commission approves Aubagio (teriflunomide) as the first oral MS therapy for first-line treatment of children and adolescents living with relapsing-remitting multiple sclerosis. Available at: www.sanofi.com/en/media-room/press-releases/2021/2021-06-18-15-45-00-2249701 (accessed 14 May 2022).
- Dale RC, Briot F, Duffy LV, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. *Neurology*. 2014;83:142–50.
- Chitnis T, Tardieu M, Amato MP, et al. International pediatric MS study group clinical trials summit: Meeting report. *Neurology*. 2013;80:1161–8.
- O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med*. 2011;365:1293–303.
- Sormani M, Waubant E. Paediatric multiple sclerosis: A lesson from TERIKIDS. *Lancet Neurol*. 2021;20:971–3.
- Wendel EM, Bertolini A, Koussoulos L, et al. Serum neurofilament light-chain levels in children with monophasic myelin oligodendrocyte glycoprotein-associated disease, multiple sclerosis, and other acquired demyelinating syndrome. *Mult Scler*. 2022;135245852210810.
- Vujosevic S, Parra MM, Hartnett ME, et al. Optical coherence tomography as retinal imaging biomarker of neuroinflammation/neurodegeneration in systemic disorders in adults and children. *Eye (Lond)*. 2022;1–17.
- Waubant E, Banwell B, Wassmer E, et al. Clinical trials of disease-modifying agents in pediatric MS: Opportunities, challenges, and recommendations from the IPMSSG. *Neurology*. 2019;92:e2538–49.
- Lagler FB, Hirschfeld S, Kindblom JM. Challenges in clinical trials for children and young people. *Arch Dis Child*. 2021;106:321–5.
- U.S. Food and Drug Administration. FDA-Approved Drugs. Available at: www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppNo=022527 (accessed 7 January 2022).
- Yamamura T, Kleiter I, Fujihara K, et al. Trial of satralizumab in neuromyelitis optica spectrum disorder. *N Engl J Med*. 2019;381:2114–24.