



# Considering the Future of Pediatric Multiple Sclerosis Trials After the CONNECT Open-Label Randomized Trial

Omar Abdel-Mannan, MD; Olga Ciccarelli, MD, PhD; Yael Hacohen, MRCPCH, Dphil

The approach to treatment of relapsing-remitting multiple sclerosis (RRMS) is rapidly evolving, with more than 15 disease-modifying therapies (DMTs) currently licensed for adults. Current treatment algorithms in children with multiple sclerosis (MS) remain heavily reliant on adult MS protocols, and most DMTs in children are prescribed off-label. Convincing evidence has increasingly emerged to support the biological rationale that effective DMTs in adult patients with MS are equally efficacious in children.<sup>1</sup> To date, only 2 randomized clinical trials of DMTs have been published in pediatric-onset MS (POMS).<sup>2,3</sup> This is partly a result of major recruitment challenges due to the low incidence and prevalence of POMS, in addition to challenges of MS diagnosis in children, with an emphasis on exclusion of other mimics, particularly antibody-mediated diseases such as myelin oligodendrocyte glycoprotein and aquaporin-4 antibodies.<sup>4</sup>

Both previously published clinical trials in POMS compared newer oral agents (teriflunomide and fingolimod) to either older injectables or placebo. In the TERIKIDS trial, conducted at 57 clinical centers in 22 countries, 109 patients (aged <18 years) were randomly assigned to teriflunomide and 57 to placebo. The study demonstrated similar efficacy of teriflunomide in a pediatric cohort compared with previous adult data, with a reduction in the adjusted number of new or enlarging T2 lesions per magnetic resonance imaging (MRI) scan by 55% and the hazard of relapse by 34% over 2 years. The PARADIGMS trial, meanwhile, enrolled 215 patients (aged <18 years) across 80 centers worldwide, with 107 patients assigned to fingolimod, and 108 to interferon  $\beta$ -1a. This study demonstrated superiority of fingolimod with a lower rate of relapse (0.12 vs 0.67,  $P < .001$ ), lower accumulation of lesions on MRI (4.39 vs 9.27,  $P < .001$ ) and a lower annualized rate of brain atrophy over a 2-year period than interferon  $\beta$ -1a. These randomized trials, however, were limited by small sample sizes (underpowered), protracted enrolment times (3 years in PARADIGMS and 3.5 years in TERIKIDS), a failure to recruit sufficient numbers of prepubertal patients (minimizing evaluation of dose-dependent responses), and a lack of long-term safety data (eg, effects on fertility in young females) given the 2-year end point. Nevertheless, both studies used MRI as a key secondary end point (both lesion load and atrophy) to overcome some of these limitations. Given the validated robust association between clinical efficacy and MRI end points,<sup>5</sup> this has important implications for the design of pediatric trials testing drugs already studied in adult MS.

In the recent CONNECT study,<sup>6</sup> Vermersch et al conducted a multicenter, active-controlled, open-label, rater-blinded randomized trial of dimethyl fumarate (an oral DMT) vs interferon  $\beta$ -1a in patients with POMS across 63 sites. The aim was to evaluate the safety and efficacy of dimethyl fumarate in children with RRMS. In total, the study included 150 patients with a median (range) age of 15.0 years (10-17); 78 were randomized to dimethyl fumarate and 72 to interferon  $\beta$ -1a. The proportion of patients free of new or newly enlarging T2 lesions at study endpoint (96 weeks) was the primary outcome measure, with secondary end points including the number of new or newly enlarging T2 lesions, proportion of relapse-free patients, annualized relapse rate, and safety. Sixty-two (79%) patients on dimethyl fumarate completed 96 weeks follow-up, and 41 (57%) of patients on interferon  $\beta$ -1a completed the trial. In the completed population, 16% of patients on dimethyl fumarate had no new or newly enlarging T2 hyperintense lesions at 96 weeks relative to baseline compared to 5% in the interferon  $\beta$ -1a group. In addition, 66% of patients on dimethyl fumarate remained relapse-free compared to 52% on interferon  $\beta$ -1a, with no significant difference

## + Related article

Author affiliations and article information are listed at the end of this article.

**Open Access.** This is an open access article distributed under the terms of the CC-BY License.

in adjusted annualized relapse rate between the two groups: 0.24; (95% CI, 0.15-0.39) for dimethyl fumarate vs 0.53 (0.33-0.84) for interferon  $\beta$ -1a. Overall safety profile between groups was comparable; number of adverse events was 74 (95%) vs 69 (96%), and serious adverse events was 8 (23%) vs 21 (29%) between dimethyl fumarate and interferon  $\beta$ -1a, respectively.

This open label study has a number of limitations. In particular, the large drop-out rate, 42% in interferon  $\beta$ -1a group and 21% in the dimethyl fumarate group, which may have led to a marginal difference in the adjusted annualized relapse rate between the two arms. Similarly, follow-up MRIs were only available in 42 of 72 for the dimethyl fumarate arm and 62 of 78 for the interferon  $\beta$ -1a arm, which is surprising in the context of a clinical trial. The addition of other imaging outcome measures, including whole brain volume and percentage change in brain volume, as reported in PARADIGMS, would also have been of interest in this study when comparing the two treatment arms. Nevertheless, the use of MRI measures as primary outcome and the long-term safety data that will be available from the ongoing extension of this study are valuable information in a rare condition such as pediatric MS.

The rapidly evolving landscape of MS therapeutics comes with significant challenges, including: (1) recruiting a sufficiently high number of children to take part in randomized trials, (2) the time and cost involved in conducting trials, and (3) trials conducted based on old medications that become obsolete by the time trials have been completed.<sup>1</sup> Our question is whether we can provide evidence of efficacy and safety in children for DMTs with a different approach. It would be attractive to rely on the efficacy of the DMTs from the adult cohorts (MS in adults and children is biologically the same disease), and provide safety data from large-scale multicenter, real-world observational cohorts, which may provide larger sample sizes, which could be used to confirm the efficacy of the medication. In parallel to this effort, factors affecting treatment response and predicting prognosis in clinical practice should be investigated in the real world of POMS. Furthermore, a shift toward using MRI outcome measures as a valid surrogate end point for clinical relapses in pediatric trials may help reduce study times when evaluating DMT efficacy, and the CONNECT trial has successfully demonstrated that this may be successful. A shift from a focusing on short-term DMT safety profiles to longer-term safety assessment (including in prepubescent patients) is recommended to ensure that treatment early in life does not expose patients to future risk. We are looking forward to part 2 of the long-term outcomes of dimethyl fumarate in patients with POMS who completed the 96-week part of the trial.

## ARTICLE INFORMATION

**Published:** September 28, 2022. doi:[10.1001/jamanetworkopen.2022.30451](https://doi.org/10.1001/jamanetworkopen.2022.30451)

**Open Access:** This is an open access article distributed under the terms of the [CC-BY License](https://creativecommons.org/licenses/by/4.0/). © 2022 Abdel-Mannan O et al. *JAMA Network Open*.

**Corresponding Author:** Yael Hachohen, MRCPCH, Dphil, Queen Square Multiple Sclerosis Centre, UCL Queen Square Institute of Neurology, Faculty of Brain Sciences, University College London, 10-12 Russell Sq, London WC1B 5EH, United Kingdom ([y.hachohen@ucl.ac.uk](mailto:y.hachohen@ucl.ac.uk)).

**Author Affiliations:** Queen Square MS Centre, UCL Queen Square Institute of Neurology, Faculty of Brain Sciences, University College London, London, United Kingdom (Abdel-Mannan, Ciccarelli, Hachohen); Department of Neurology, Great Ormond Street Hospital for Children, London, United Kingdom (Abdel-Mannan, Hachohen); NIHR University College London Hospitals Biomedical Research Centre, London, United Kingdom (Ciccarelli).

**Conflict of Interest Disclosures:** Dr Ciccarelli reported personal fees from Merck and Novartis outside the submitted work. No other disclosures were reported.

## REFERENCES

1. Hachohen Y, Banwell B, Ciccarelli O. What does first-line therapy mean for paediatric multiple sclerosis in the current era? *Mult Scler*. 2021;27(13):1970-1976. doi:[10.1177/1352458520937644](https://doi.org/10.1177/1352458520937644)
2. Chitnis T, Arnold DL, Banwell B, et al; PARADIGMS Study Group. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. *N Engl J Med*. 2018;379(11):1017-1027. doi:[10.1056/NEJMoa1800149](https://doi.org/10.1056/NEJMoa1800149)

3. Chitnis T, Banwell B, Kappos L, et al; TERIKIDS Investigators. Safety and efficacy of teriflunomide in paediatric multiple sclerosis (TERIKIDS): a multicentre, double-blind, phase 3, randomised, placebo-controlled trial. *Lancet Neurol*. 2021;20(12):1001-1011. doi:[10.1016/S1474-4422\(21\)00364-1](https://doi.org/10.1016/S1474-4422(21)00364-1)
4. Waubant E, Banwell B, Wassmer E, et al; IPMSSG. Clinical trials of disease-modifying agents in pediatric MS: Opportunities, challenges, and recommendations from the IPMSSG. *Neurology*. 2019;92(22):e2538-e2549. doi:[10.1212/WNL.0000000000007572](https://doi.org/10.1212/WNL.0000000000007572)
5. Sormani MP, Bruzzi P. MRI lesions as a surrogate for relapses in multiple sclerosis: a meta-analysis of randomised trials. *Lancet Neurol*. 2013;12(7):669-676. doi:[10.1016/S1474-4422\(13\)70103-0](https://doi.org/10.1016/S1474-4422(13)70103-0)
6. Vermersch P, Scaramozza M, Levin S, et al. Effect of dimethyl fumarate vs interferon  $\beta$ -1a in patients with pediatric-onset multiple sclerosis: the CONNECT randomized clinical trial. *JAMA Netw Open*. 2022;5(9):e2230439. doi:[10.1001/jamanetworkopen.2022.30439](https://doi.org/10.1001/jamanetworkopen.2022.30439)