Pediatric multiple sclerosis

Escalation and emerging treatments

Tanuja Chitnis, MD
Angelo Ghezzi, MD
Barbara Bajer-Kornek, MD
Alexey Boyko, DSc
Gavin Giovannoni, PhD, FRCP
Daniela Pohl, MD, PhD

Correspondence to Dr. Chitnis: tchitnis@partners.org

ABSTRACT

Over the last 20 years, there have been significant advances in multiple sclerosis (MS) therapeutics, with regulatory approval for 13 therapies in adults by the European Medicines Agency (EMA) and Food and Drug Administration. However, there is only limited approval for interferon-β and glatiramer acetate use in children 12 years and older by the EMA. Availability of disease-modifying therapies to children and adolescents with MS is variable by region, and is extremely limited in some regions of the world. Up to 30% of children experience breakthrough disease requiring therapies beyond traditional first-line agents. Recent legislation in both the United States and Europe has mandated clinical studies for all new therapeutics applicable to children. Several clinical trials in children are underway that will provide important information regarding the efficacy and safety of newer drugs. This review summarizes the current knowledge of breakthrough disease, escalation, and induction treatment approaches in children with MS, especially pertaining to disease course and disability outcomes in this group of patients. In addition, ongoing clinical trials and approaches and challenges in conducting clinical trials in the pediatric population are discussed. *Neurology*® 2016;87 (Suppl 2):S103–S109

GLOSSARY

AOMS = adult-onset multiple sclerosis; **ARR** = annualized relapse rate; **CI** = confidence interval; **EDSS** = Expanded Disability Status Scale; **EMA** = European Medicines Agency; **FDA** = Food and Drug Administration; **GA** = glatiramer acetate; **IFN** = interferon; **IPMSSG** = International Pediatric MS Study Group; **JCV** = JC virus; **MS** = multiple sclerosis; **NEDA** = no evident disease activity; **NMO** = neuromyelitis optica; **PIP** = Pediatric Investigation Plan; **PML** = progressive multifocal leukoencephalopathy; **POMS** = pediatric-onset multiple sclerosis; **PREA** = Pediatric Research Equity Act.

Over the last 20 years, there have been significant advances in multiple sclerosis (MS) therapeutics, with regulatory approval for 13 therapies in adults by the European Medicines Agency (EMA) and Food and Drug Administration (FDA).[1] There is limited approval for interferon (IFN)–β and glatiramer acetate (GA) use in children ≥12 years of age by the EMA. Safety data for IFN–β-1a SC TIW (Rebif) for children >2 years of age is included in the European label. Availability of disease-modifying therapies to children and adolescents with MS is variable by region, and is extremely limited in some regions of the world. Several clinical trials in children are underway that will bring important information regarding the efficacy and safety of newer drugs (table 1). This review summarizes the current knowledge of breakthrough disease, escalation, and induction treatment approaches in children with MS, especially pertaining to disease course and disability outcomes in this group of patients.

CONCEPTUAL APPROACHES TO TREATING CHILDREN WITH MS

No evident disease activity (NEDA). The ultimate goal of therapy in MS is to prevent relapses and to halt disability accrual. The concept of zero disease activity has been termed NEDA, measured by absence of clinical and MRI disease,[2,3] and is increasingly being viewed as the overall goal for treatment. However, the impact of low subclinical disease activity (e.g., rare new lesions on MRI) on long-term MS outcome is unclear. Despite advances in MS therapeutics, no one MS therapy has 100% efficacy on NEDA, and NEDA is achieved in approximately 50% of adult patients with MS followed for 2 years in any therapeutic trial.[4] Longitudinal data have shown that only 7% of adult patients with

From Partners Pediatric MS Center (T.C.), Massachusetts General Hospital, Harvard Medical School, Boston; Divisione di Neurologia 2–Centro Studi Sclerosi Multipla (A.G.), Ospedale di Gallarate, Italy; Department of Neurology (B.B.-K.), Medical University of Vienna, Austria; Department of Neurology, Neurosurgery and Medical Genetics (A.B.), Pirogov's Russian National Research Medical University, Moscow; Barts and The London School of Medicine and Dentistry (G.G.), London, UK; and Department of Neurology (D.P.), Children's Hospital of Eastern Ontario, University of Ottawa, Canada.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Table 1 Current interventional clinical trials in pediatric multiple sclerosis (MS) (listed on clinicaltrials.gov, search term pediatric MS, June 2015)

Study drug	Comparator	Design	Phase	Primary outcome measure	Secondary outcome measures	Estimated enrollment	Start date	Anticipated end date	Sponsor and NCT no.
Fingolimod (Gilenya)	Interferon β-1a IM (Avonex)	Randomized controlled, double-blind, double dummy masked	3	ARR	PK, MRI outcomes, cognitive battery	190	July 2013	September 2017	Novartis NCT01892722
Teriflunomide (Aubagio)	Placebo	Randomized controlled, double-blind	3	Time to first clinical relapse after randomization	PK, MRI outcomes, cognitive battery	165	July 2014	January 2020	Sanofi NCT02201108
Dimethyl fumarate (Tecfidera)	None	Open-label	2	Change in the number of new or newly enlarging T2 hyperintense lesions on brain MRI scans from the baseline period to on-treatment assessment period	PK measures	18	July 2015	July 2016	Biogen Idec NCT02410200
Dimethyl fumarate (Tecfidera)	Interferon β-1a IM (Avonex)	Open-label, randomized	3	Proportion of participants free of new/newly enlarging T2 hyperintense lesions on brain MRI scans	MRI outcomes, cognitive battery	142	August 2014	September 2020	Biogen Idec NCT02283853
Dimethyl fumarate (Tecfidera)	Placebo	Open-label, randomized	3	Time to first clinical relapse	MRI outcomes, cognitive battery	172	December 2015	January 2027	Biogen Idec NCT02428218
Natalizumab (Tysabri)	None	Open-label	1	PK measures	PD measures	13	July 2013	July 2014	Biogen Idec NCT01884935
IR902 TCR peptide formulation in IFA BV5S2, BV6S5 BV13S1 (Neurovax)	Incomplete Freund's adjuvant	Randomized, double-blind	1	New MRI Gd+ lesions; WBC measurements	Immune measures, EDSS score	12	November 2016	November 2018	Immune Response Pharma Inc. NCT02200718

Abbreviations: ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; PD = pharmacodynamics; PK = pharmacokinetics; Gd+ = gadolinium-enhancing lesions; WBC = white blood cells.

MS remain NEDA at 7 years of follow-up.[4] NEDA has not yet been systematically evaluated in children with MS, especially since formal clinical trials in this population have only just started, and there are limited longitudinal datasets available to answer this question. Although difficult to achieve on a population or cohort level, NEDA is the ultimate goal for individual treatment in pediatric MS. However, given the current treatment options and available treatment data in pediatric MS, this may be challenging to achieve in all patients.

Individualized therapy. The identification of patients with high and low risk for disease activity and disability accrual falls into the overall concept of personalized or individualized medicine, which should also be considered in pediatric MS, particularly as more therapies become available. Validated outcome predictors are limited in adults and nonexistent in children with MS.

Induction vs escalation therapy. Another relevant concept when considering approaches to treating pediatric MS is the idea of stepwise escalation in therapy vs initiation with potent agents, which, if followed by de-escalation, can be termed induction therapy. There is presently insufficient evidence in adult and pediatric MS to favor one approach over another, and consideration of the overall disease course, safety, and efficacy of various drugs currently guides therapeutic decisions. The terminology of first- and second-line treatments is disappearing in the academic literature and is being supplanted with the concepts of escalation/induction and individualized therapy; however, the terms first/second-line treatments are still often used by payers and regulatory agencies.

SHORT- AND LONG-TERM CONSEQUENCES OF PEDIATRIC MS As summarized in "Pediatric multiple sclerosis: Clinical features and outcome" (p. S74), pediatric MS appears to be overall a more inflammatory disease than adult MS, with more frequent relapses[5,6] and MRI lesion accrual.[7] Paradoxically, long-term disability accrual measured by the Expanded Disability Status Scale is slower in pediatric-onset MS (POMS) than adult-onset MS (AOMS); however, patients with POMS will be more disabled than patients with AOMS at a younger age.[8] Between 30% and 50% of children with MS experience significant cognitive issues (see "Pediatric multiple sclerosis: Cognition and mood," p. S82), and adults with POMS may have more difficulty with processing speed than patients with AOMS.[9] Given that children experience MS during a critical point in their overall brain, cognitive, social, and educational development, outcomes tailored to pediatric MS should be considered. Therefore, when evaluating therapeutic efficacy in children with MS, these factors, and particularly cognition, should be taken into account.

INADEQUATE TREATMENT RESPONSE TO INITIAL THERAPY The current knowledge on treatment with IFN and GA in children, which have been the most commonly used therapies in pediatric MS over the last 10 years, is summarized in "Pediatric multiple sclerosis: Conventional first-line treatment and general management" (p. S97). IFNs and GA are reported to decrease the relapse rate in adult patients with MS by approximately 30%. In absence of placebo-controlled double-blind treatment studies, several retrospective or open-label studies in children treated with IFN or GA have demonstrated similar or greater reductions in relapse rates. However, as in adult patients with MS, many children experience breakthrough disease.

Definitions for inadequate treatment response vary and have to take into account age (higher relapse rates in pediatric than adult patients with MS), disease duration (relapse rate declines over time), and disease activity prior to treatment initiation. A recent International Pediatric MS Study Group (IPMSSG) consensus statement proposes the following definition of inadequate treatment response in pediatric MS: if the patient has been fully compliant on treatment for at least 6 months and demonstrates (1) no reduction in relapse rate or new T2 or contrast-enhancing lesions (as compared to pretreatment); or (2) 2 or more confirmed relapses (clinical or MRI) within a 12-month period.[10] This definition might be conservative with regards to relapse activity, and another review has suggested that an annual relapse rate >0.6 in the first 2 years of disease or >0.35 in years 2–5, or ≥3 new lesions in the first year and >2 lesions in years 2 and 3, would indicate inadequate treatment response.[11]

None of these definitions has formally been applied to pediatric MS cohorts, and the percentage of children with inadequate treatment response is therefore unknown. A retrospective analysis of 258 treated pediatric patients with MS revealed that 28% were considered by their health care practitioners to have refractory disease on their first therapy (mainly IFN and GA), and were therefore switched to a second therapy after a mean of 1.3 years. Medication changes included lateral switches between IFN and GA therapies, as well as use of natalizumab, daclizumab, and cyclophosphamide, among others.

Adherence. Medication switches on account of poor tolerance or noncompliance were reported in 16% of patients after mean treatment duration of 1.1 years.[12] Self-reported rate of nonadherence (defined as not taking the prescribed medication >20% over the past month) was as high as 37%[13]–47%[14] in recent surveys of pediatric patients with MS. A Russian study found that in adolescents with MS, adherence was better in therapies with fewer weekly injections.[15] In the absence of reliable biological adherence markers, discrimination between inadequate treatment responses secondary to refractory disease or secondary to nonadherence remains a major challenge. Use of clinic-administered therapies or oral therapies could potentially increase adherence, particularly in the adolescent population, and should be a focus for further study.

CURRENT KNOWLEDGE ON SECOND-LINE TREATMENTS IN PEDIATRIC MS None of the currently available immunomodulatory or immunosuppressive treatments in use for adult patients with highly active relapsing-remitting MS has completed randomized controlled trials in the pediatric population. However, the increasing number of published reports of second-line agent use in children and adolescents with MS confirms the need for additional therapies in this age group.

Natalizumab. Natalizumab, a humanized monoclonal antibody targeting the α4 subunit of α4β1 integrin, was first introduced in 2004. In its pivotal randomized controlled phase III trial, it demonstrated a 68% reduction of the annualized relapse rate (ARR) ($p < 0.001$), a 42% reduction of 12 weeks sustained progression of disability ($p < 0.001$), and an 83% reduction of new T2 lesions on MRI compared to placebo ($p < 0.001$).[16] However, 3 months after its initial approval, natalizumab was temporarily withdrawn from the market, following the occurrence of 3 cases of progressive multifocal leukoencephalopathy (PML).[17–19] Natalizumab was reintroduced for the second time into the US market and the European Union in 2006, with the stipulation of a Global Risk Management Plan, mandated in the United States (TOUCH: TYSABRI Outreach: Unified Commitment to Health) and voluntarily in the rest of the world (TYGRIS: TYSABRI Global Observation Program in Safety). Three risk factors for PML associated with natalizumab use have been identified: (1) positive serostatus for anti–JC virus (JCV) antibodies; (2) prior use of immunosuppressants; (3) duration of natalizumab therapy.[20] The overall PML incidence, as of June 3, 2015, in natalizumab-treated patients was 3.96 cases/1,000 patients (95% confidence interval [CI] 3.64–4.30 per 1,000 patients), with the highest risk in JCV-positive patients who have received prior immunosuppression and treatment duration of >24 months (11.2/1,000; 95% CI

8.6–14.3).[21] The recently published long-term studies (Safety of TYSABRI Redosing and Treatment, Tysabri Observational Program) confirmed no additional serious adverse events, other than PML.[22,23]

Natalizumab use in pediatric MS was reported in several retrospective series.[24–28] In an Italian report of 55 cases, natalizumab was started at a mean age of 14.4 ± 2.6 years after a mean disease duration of 25.5 ± 19.2 months.[24] ARR decreased from 2.4 ± 1.6 in the year before natalizumab therapy to 0.1 ± 0.2 at the end of the treatment period (p = 0.001). Median Expanded Disability Status Scale (EDSS) decreased from 2.5 (range 1–6.5) at treatment initiation to 1.5 (range 0–5) at last visit. Sixty percent of patients were free from clinical and MRI activity after 30 months of treatment. A German/Austrian cohort including 20 pediatric patients[26] treated with natalizumab led to profound reduction of the ARR (3.7 vs 0.4; $p < 0.004$) and median EDSS score (2 vs 1; $p < 0.024$). The frequency of anti-JCV antibodies was 39%[24] and 38%,[26] which is lower compared to the reported prevalence in adults of 57%. Side effects were mild to moderate in both series and comprised infections and hypersensitivity. Neutralizing antibodies were found in 2 out of 16 patients.[17] In both cases, natalizumab was withdrawn due to a severe relapse or anaphylaxis. Interestingly, a German study found that 50% of their pediatric patients with MS overall were JCV antibody–positive, which was considerably higher than reported in other studies.[25]

Discontinuation of natalizumab is often associated with return of clinical and MRI activity. In 6 out of 8 pediatric patients who discontinued natalizumab, ≥1 relapse occurred within the following 6 months.[26]

Mitoxantrone. Mitoxantrone is approved for adult patients with rapidly evolving relapsing-remitting and secondary progressive MS according to the MIMS trial.[29] However, mitoxantrone is associated with increased risk of cardiomyopathy in up to 12% of patients,[30] therapy-related acute leukemia (up to 2.8%[31]), liver toxicity, and amenorrhea, and therefore is rarely used. One report documents mitoxantrone use in 4 pediatric patients with MS with 3.8–18 years of follow-up.[32] Laboratory abnormalities including anemia, leukopenia, and elevation of liver enzymes returned to normal levels after cessation of therapy. One patient developed transient asymptomatic left ventricular dysfunction during treatment. Leukemia was not reported in this case series; however, cardiomyopathy and leukemia may occur many years after treatment cessation.[30]

Cyclophosphamide. Cyclophosphamide has been used mainly as a second- or third-line agent in very active MS. Although formal approval has not been achieved, cyclophosphamide may be effective in reducing clinical and MRI activity. Cyclophosphamide therapy is associated with significant safety concerns, including an increased risk of bladder cancer as well as the risk of secondary leukemia and infertility. A retrospective multicenter study reported treatment of 17 pediatric patients with severe relapses or ongoing relapse activity despite conventional therapy.[33] Before the onset of cyclophosphamide therapy, the 14 patients had a mean of 3.8 relapses per year, which decreased to 1.1 during the first year of cyclophosphamide therapy. Seven patients remained relapse-free. The EDSS remained stable or decreased in 10 out of 12 patients. After cessation of therapy, 50% of patients with a follow-up of more than 1 year experienced relapses and required further second-line therapies. Short-term side effects included nausea and vomiting in 15/17 patients, alopecia in 10/17 patients, and menstrual irregularities in 5 patients, as well as anemia and thrombocytopenia. Lymphopenia was achieved in all children, according to therapy goals. Long-term side effects included the development of bladder cancer in one patient, amenorrhea in 3 girls, and sterility in one patient. Secondary leukemia was not reported in these cases.

Rituximab. Rituximab is an anti-CD20 chimeric monoclonal antibody that has been shown to suppress clinical and MRI activity in MS and neuromyelitis optica (NMO). A retrospective review documents rituximab use in 144 children and adolescents with pediatric autoimmune and inflammatory disorders of CNS: NMDA receptor encephalitis (n = 39), opsoclonus myoclonus ataxia syndrome (n = 32), NMO (n = 20), MS (n = 4), neuropsychiatric systemic lupus erythematosus (18), and other neuroinflammatory disorders (n = 35).[34] A definite, probable, or possible benefit was reported in 125 of 144 (87%) patients. Rituximab improved neurologic outcomes with a 7.6% risk of transient adverse infectious events. A separate retrospective study reported rituximab therapy in 11 pediatric patients, including 8 patients with NMO and 3 patients with MS.[35] Two out of the 3 children with MS remained relapse-free on follow-up while 1 patient continued to experience relapses. The treatment was well-tolerated and no serious infections occurred. Another report of 14 Swedish pediatric MS patients (mean age 16.5 years) found rituximab treatment to be safe and well-tolerated. None of the patients experienced new relapses after a median treatment duration of 23.6 months.[36] A related agent is ocrelizumab, a fully humanized monoclonal antibody to CD20, which completed phase III trials in adult relapsing-remitting MS in 2015.

Fingolimod. Fingolimod has had some limited use in children. A retrospective review from Brazil documented 17 children between the ages of 14 and 17 treated with fingolimod. Mean pretreatment ARR was 2.8, EDSS was 2.05 ± 0.98. Patients were followed for a mean of 8.6 months (range 1–18 months). Only one patient had a relapse 14 months after starting treatment. Of the 12 patients with an MRI 3–6 months after the start of treatment, 1 patient had a new lesion. No major adverse events were noted in this study.[37]

Several drugs are currently in clinical trials for pediatric MS (table 1). Ongoing trials include those for 3 oral therapies, which are approved for adult MS by the EMA and FDA: fingolimod, dimethyl fumarate, and teriflunomide. Mechanism of action and adverse events observed in adult MS are provided in table 2.

CONCEPTS AROUND EMERGING CLINICAL TRIALS OF NOVEL AGENTS IN PEDIATRIC MS

All the pediatric MS treatment studies published to date are observational studies. However, federal mandates from the US Congress introduced in 2003 and amended in 2007 and similar mandates from the European Union in 2008 require pediatric studies to be performed for all new therapies. In the United States, the Pediatric Research Equity Act (PREA) passed in 2003 required a pediatric assessment for certain applications unless waived or deferred. The PREA was amended in 2007 to apply to any new active ingredient, indication, dosage form, regimen, or route. Waivers are granted if drug will not be used substantially in children, or if ineffective or unsafe in children, or if formulation cannot be made. An accompanying piece of legislation termed the Best Pharmaceuticals for Children Act was passed in 2002 and amended in 2007, and allowed the voluntary submission of a written request if studies are needed in the pediatric population, allowing the sponsor 6 months of additional marketing exclusivity. Similarly, the EMA and its pediatric committee, the PDCO, advises on Pediatric Investigation Plans (PIPs). As of July 2008, the condition for registering a new drug is an agreed-upon PIP. Similar to the written request, compliance with the PIP is rewarded by 6 months of additional market exclusivity.

Given these mandates, the need for randomized clinical trials in pediatric MS was recognized. The IPMSSG published 2 consensus statements around this topic. The first, published in 2012,[10] summarized consensus from 50 IPMSSG members and concluded the following:

- Exposure of pediatric patients with MS to new therapeutic agents should occur in the context of carefully designed clinical trials.
- Placebo-controlled trials in pediatric MS should be of brief duration and should have rigorous monitoring to ensure a rescue strategy for children in the placebo arm who experience rapid accrual of physical, cognitive, or MRI burden of disease.
- Development and growth parameters should be included in all studies, as well as long-term impact on fertility.
- Contraceptive use and close pregnancy monitoring should be considered for female patients of child-bearing potential.

The second article is a summary statement from a meeting held in January 2012[1] with representatives from the FDA, EMA, Health Canada, academic neurologists, and representatives from pharmaceutical companies. The major additional conclusions were as follows:

- Randomized controlled trials are necessary from a regulatory standpoint for drug approval, and will provide robust data to guide clinical care.
- Patient study populations should include <10-year-old participants.
- Relapse is a clinically meaningful outcome measure for trials meeting regulatory requirements.
- Inclusion of an internationally applicable neuropsychological battery for pediatric MS that is sensitive to cognitive deficits in pediatric MS and suited for detecting reliable change is needed.

Table 2 Dosing and potential adverse events for oral agents currently in clinical trials in pediatric multiple sclerosis (MS)

Name	Route/adult dosing schedule	Mechanism of action	Adverse events observed in adult MS
Fingolimod	Oral/once daily	Sphingosine-1-phosphate receptor modulator, which prevents lymphocyte from lymph nodes	Bradycardia at first dose, varicella infections, herpetic infections, macular edema, lymphopenia, PML (rare)
Dimethyl fumarate	Oral/twice daily	Nrf2 antioxidant pathway modulator	Flushing after dosing, GI upset, lymphopenia, PML (rare)
Teriflunomide	Oral/once daily	Reversible inhibition of dihydroorotate dehydrogenase, a mitochondrial enzyme involved in pyrimidine synthesis for DNA replication, affecting T- and B-cell proliferation	Hair loss, liver test abnormalities

Abbreviations: GI = gastrointestinal; PML = progressive multifocal leukoencephalopathy.

- A prospective registry is needed to obtain data on safety and clinical outcome in patients exposed to MS therapies during childhood to evaluate long-term impact.

Various aspects of clinical trial design were discussed, including the use of placebo vs active comparator and ARR vs time to relapse designs, as well as estimated sample sizes needed for these various designs. Since then, several clinical trials in pediatric MS have been launched, and their design and specifics are summarized in table 1.

VIEW TO FUTURE APPROACHES TO THERAPY WITH CURRENTLY AVAILABLE AND EMERGING KNOWLEDGE OF THERAPEUTICS IN PEDIATRIC MS Apart from those listed in table 1, additional therapies are in or have completed late-stage trials in adult MS. Many of these newer agents will require pediatric studies. Some considerations for moving forward with such studies are listed in table 3.

The emergence of newer classes of drugs that are being developed for MS, including remyelinating therapies,[38] neuroprotective therapies,[39] and symptomatic treatments,[40] presents new opportunities and challenges when considering use in pediatric MS. Some of these classes will apply to children, and consideration of outcome measure for pediatric studies is critical for effective evaluation of these therapies.

The most important factor to keep in mind when considering long-term treatment is how therapies impact pediatric patients and their families over the short and long term. A major need is a means to evaluate the long-term outcomes of therapies on the physical, developmental, cognitive, and psychosocial outcomes in patients with childhood-onset MS into adulthood, potentially through the implementation of long-term outcomes registries. International collaboration among physicians, patients and their families, regulators, and the pharmaceutical industry is required in all of the aspects discussed above.

Table 3 Considerations for future clinical trials in pediatric multiple sclerosis (MS)

1. There are a limited number of children worldwide with MS; therefore it is recommended that only one phase III trial be initiated for each agent, and to avoid the situation of multiple studies, possibly to satisfy different regulators, for one drug. Wherever possible, all international trials should be harmonized.
2. Pharmacokinetic and pharmacodynamics studies should precede and inform dosing for phase II/III trials.
3. There is a need for increased awareness and training of clinicians treating children with MS in clinical trial methodology and understanding the risks and benefits that clinical trials offer.
4. Further discussions with patients and their families regarding their goals for treatment and clinical trials and to develop patient-centered outcomes are needed.
5. Continued discussion and information about the state of the field for regulators and the pharmaceutical industry is required.
6. There is a need to explore strategies to facilitate and expedite clinical trials in pediatric MS.
7. Methodology to evaluate long-term safety and efficacy outcomes in pediatric patients with MS, particularly those participating in clinical trials, is needed.

AUTHOR CONTRIBUTIONS

All authors contributed to the drafting, revising, and review of this article.

STUDY FUNDING

This supplement is made possible by funding from the MS Cure Fund, Danish MS Society, German MS Society, Italian MS Association, MS International Federation, MS Research Foundation (Netherlands), National MS Society (USA) and Swiss MS Society.

DISCLOSURE

T. Chitnis has received personal compensation for advisory board/consulting for Biogen-Idec, Merck-Serono, and Novartis, and has received research support from Merck-Serono and Novartis Pharmaceuticals. She serves on pediatric clinical trial advisory boards for Genzyme-Sanofi and Novartis. A. Ghezzi has received honoraria for speaking from Biogen-Idec, Merck-Serono, Novartis, Genzyme, Teva, and Allergan, and for consultancy from Merck-Serono, Teva, Novartis, and Biogen-Idec; and received support for participation in the National and International Congresses from Schering, Biogen-Idec, Merck-Serono, Novartis, Genzyme, and Teva. B. Bajer-Kornek has received honoraria for speaking from Genzyme, Biogen-Idec, Teva, Merck-Serono, Novartis, Bayer, and Merck-Serono and for consultancy from Genzyme, Merck-Serono, and Bayer. A. Boyko has received personal compensation for advisory board/consulting and participated in clinical trials sponsored by for Biogen-Idec, Merck-Serono, TEVA, Genzyme-Sanofi, and Novartis. G. Giovannoni has participated in the following: AbbVie: steering committee member on the Daclizumab trials; Biogen-Idec: steering committee member on the BG12 and Daclizumab trials; has received consultancy fees for advisory board meetings, honoraria for speaking at Physicians summit, GSK consultancy fees in relation to their phase 3 MS trial program, and consultancy fees for advisory board meetings from Merck-Serono; was a steering committee member for Novartis on fingolimod and siponimod trials; received consultancy fees for advisory board meetings; and was a steering committee member for Teva. D. Pohl has received compensation for consulting or conference presentations from Bayer, Biogen-Idec, Merck-Serono, and Teva. Go to Neurology.org for full disclosures.

Received August 19, 2015. Accepted in final form February 18, 2016.

REFERENCES

1. Chitnis T, Tardieu M, Amato MP, et al. International Pediatric MS Study Group Clinical Trials Summit: meeting report. Neurology 2013;80:1161–1168.
2. Stangel M, Penner IK, Kallmann BA, Lukas C, Kieseier BC. Towards the implementation of "no evidence of disease activity" in multiple sclerosis treatment: the multiple sclerosis decision model. Ther Adv Neurol Disord 2015;8:3–13.
3. Bevan CJ, Cree BA. Disease activity free status: a new end point for a new era in multiple sclerosis clinical research? JAMA Neurol 2014;71:269–270.
4. 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;72:152–158.
5. Gorman MP, Healy BC, Polgar-Turcsanyi M, Chitnis T. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. Arch Neurol 2009;66:54–59.
6. Benson LA, Healy BC, Gorman MP, et al. Elevated relapse rates in pediatric compared to adult MS persist for at least 6 years. Mult Scler Relat Disord 2014;3:186–193.
7. Yeh EA, Weinstock-Guttman B, Ramanathan M, et al. Magnetic resonance imaging characteristics of children and adults with paediatric-onset multiple sclerosis. Brain 2009;132:3392–3400.

8. Renoux C, Vukusic S, Mikaeloff Y, et al. Natural history of multiple sclerosis with childhood onset. N Engl J Med 2007;356:2603–2613.
9. Baruch NF, O'Donnell EH, Glanz BI, et al. Cognitive and patient-reported outcomes in adults with pediatric-onset multiple sclerosis. Mult Scler 2016;22:354–361.
10. Chitnis T, Tenembaum S, Banwell B, et al. Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis. Mult Scler 2012;18:116–127.
11. Banwell B, Bar-Or A, Giovannoni G, Dale RC, Tardieu M. Therapies for multiple sclerosis: considerations in the pediatric patient. Nat Rev Neurol 2011;7:109–122.
12. Yeh EA, Waubant E, Krupp LB, et al. Multiple sclerosis therapies in pediatric patients with refractory multiple sclerosis. Arch Neurol 2011;68:437–444.
13. Lulu S, Julian L, Shapiro E, Hudson K, Waubant E. Treatment adherence and transitioning youth in pediatric multiple sclerosis. Mult Scler Relat Disord 2014;3:689–695.
14. Thannhauser JE, Mah JK, Metz LM. Adherence of adolescents to multiple sclerosis disease-modifying therapy. Pediatr Neurol 2009;41:119–123.
15. Boiko AN, Batysheva TT, Bykova OV, et al. The comparative study of efficacy and tolerability of intramuscular introduction of beta-interferon-1a in adults and adolescents with remitting multiple sclerosis [in Russian]. Zh Nevrol Psikhiatr Im S S Korsakova 2012;112:98–103.
16. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;354:899–910.
17. Langer-Gould A, Atlas SW, Bollen AW, Pelletier D. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. N Engl J Med 2005;353:375–381.
18. Kleinschmidt-Demasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. N Engl J Med 2005;353:369–374.
19. Van Assche G, Van Ranst M, Sciot R, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. N Engl J Med 2005;353:362–368.
20. Bloomgren G, Richman S, Hotermans C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N Engl J Med 2012;366:1870–1880.
21. Plavina T, Subramanyam M, Bloomgren G, et al. Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. Ann Neurol 2014;76:802–812.
22. O'Connor P, Goodman A, Kappos L, et al. Long-term safety and effectiveness of natalizumab redosing and treatment in the STRATA MS Study. Neurology 2014;83:78–86.
23. Magdolna S. Effectiveness and safety of natalizumab in multiple sclerosis: data of the first five years from the TOP (Tysabri Observational Program) [in Hungarian]. Ideggyogy Sz 2014;67:211–212.
24. Ghezzi A, Pozzilli C, Grimaldi LM, et al. Natalizumab in pediatric multiple sclerosis: results of a cohort of 55 cases. Mult Scler 2013;19:1106–1112.
25. Huppke P, Stark W, Zurcher C, Huppke B, Bruck W, Gartner J. Natalizumab use in pediatric multiple sclerosis. Arch Neurol 2008;65:1655–1658.
26. Kornek B, Aboul-Enein F, Rostasy K, et al. Natalizumab therapy for highly active pediatric multiple sclerosis. JAMA Neurol 2013;70:469–475.
27. Putzki N, Stich O, Gartzen K, Kastrup O, Tettenborn B, Rauer S. Natalizumab treatment in paediatric multiple sclerosis: a case of induction, de-escalation and escalation. Eur J Neurol 2010;17:e105.
28. Arnal-Garcia C, Garcia-Montero MR, Malaga I, et al. Natalizumab use in pediatric patients with relapsing-remitting multiple sclerosis. Eur J Paediatr Neurol 2013;17:50–54.
29. Hartung HP, Gonsette R, Konig N, et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. Lancet 2002; 360:2018–2025.
30. Marriott JJ, Miyasaki JM, Gronseth G, O'Connor PW; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Evidence Report: the efficacy and safety of mitoxantrone (Novantrone) in the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2010;74: 1463–1470.
31. Pascual AM, Tellez N, Bosca I, et al. Revision of the risk of secondary leukaemia after mitoxantrone in multiple sclerosis populations is required. Mult Scler 2009;15:1303–1310.
32. Kornek B, Bernert G, Rostasy K, et al. Long-term follow-up of pediatric patients treated with mitoxantrone for multiple sclerosis. Neuropediatrics 2011;42:7–12.
33. Makhani N, Gorman MP, Branson HM, Stazzone L, Banwell BL, Chitnis T. Cyclophosphamide therapy in pediatric multiple sclerosis. Neurology 2009;72:2076–2082.
34. Dale RC, Brilot F, Duffy LV, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology 2014;83:142–150.
35. Beres SJ, Graves J, Waubant E. Rituximab use in pediatric central demyelinating disease. Pediatr Neurol 2014;51: 114–118.
36. Salzer J, Lycke J, Wickstrom R, Naver H, Piehl F, Svenningsson A. Rituximab in paediatric onset multiple sclerosis: a case series. J Neurol 2015;263:322–326.
37. Fragoso YD, Alves-Leon SV, Barreira AA, et al. Fingolimod prescribed for the treatment of multiple sclerosis in patients younger than age 18 years. Pediatr Neurol 2015; 53:166–168.
38. Hartley MD, Altowaijri G, Bourdette D. Remyelination and multiple sclerosis: therapeutic approaches and challenges. Curr Neurol Neurosci Rep 2014;14:485.
39. Rottlaender A, Kuerten S. Stepchild or prodigy? Neuroprotection in multiple sclerosis (MS) research. Int J Mol Sci 2015;16:14850–14865.
40. Toosy A, Ciccarelli O, Thompson A. Symptomatic treatment and management of multiple sclerosis. Handb Clin Neurol 2014;122:513–562.