

Treatment of pediatric multiple sclerosis and variants

D. Pohl, MD*; E. Waubant, MD, PhD*; B. Banwell, MD; D. Chabas, MD, PhD; T. Chitnis, MD; B. Weinstock-Guttman, MD; and S. Tenembaum, MD; for the International Pediatric MS Study Group‡

Abstract—Studies in adult patients with multiple sclerosis (MS) suggest significant benefit of early treatment initiation. However, there are no approved therapies for children and adolescents with MS. For adult MS, tolerability and efficacy of several immunomodulatory and immunosuppressive drugs have been demonstrated. Guidelines for the use of these MS therapies in children do not exist. Several small cohort studies of the safety and tolerability of disease-modifying therapies (DMT) in children and adolescents with MS have been recently reported. The side effects of interferon beta (IFNB) and glatiramer acetate (GA) appear to be similar to those reported by adults. The long-term tolerability and safety have yet to be established and efficacy data have yet to be studied. In view of the potential for significant long-term physical and cognitive disability in children with MS, and recent evidence that initiation of immunomodulatory therapy early in the course of MS improves long-term prognosis, an increasing number of children and adolescents with MS are being offered the DMT approved for adults. This review summarizes current knowledge of DMT in pediatric MS and experience in several centers treating pediatric MS and MS variants such as neuromyelitis optica or Devic disease, Balo concentric sclerosis, Marburg acute MS, and Schilder disease (myelinoclastic diffuse sclerosis). Finally, an overview of symptomatic MS therapies and experiences with these treatments in pediatric patients is provided.

NEUROLOGY 2007;68(Suppl 2):S54–S65

Pediatric multiple sclerosis (MS) is often associated with a relatively high relapse rate early in the disease. However, the conversion to a secondary progressive course or long-term disability is thought to be slower in children compared to adults. Nonetheless, as a result of developing MS at an early age, individuals reaching any given level of impairment will be younger than individuals with adult onset disease.^{1,2}

Disease-modifying therapies (DMT) for adult MS are now initiated soon after diagnosis based on several clinical trials that suggested benefits of early treatment.^{3–5} Patients younger than 18 years were not enrolled in pivotal trials of MS therapies, and thus these therapies have not been officially approved in the pediatric age group. Since there appears to be considerable overlap between MS in children, adolescents, and adults,⁶ many young patients are already receiving off label treatment with DMT approved for adult MS.

Children and adolescents treated with immunomodulating drugs seem to experience similar side effects as adult MS patients.^{7–11} However, because of weight and body surface differences, it is not clear how the dosage should be adapted to maximize tolerability and efficacy for individuals before they reach

adult size. Furthermore, general questions such as drug effect on growth, puberty, or long-term adverse events on the still immature immune system have not yet been addressed. In addition, since all immunomodulating drugs are relatively new (maximum experience of about 15 years in adults), unexpected long-term adverse events remain possible and could be of particular importance in younger patients.

Current MS therapies. The aim of drugs that modify the course of MS is to reduce the frequency of clinical relapses and to prevent the progression of disability. Current DMTs for MS modulate or suppress the immune system (table 1). There are four Food and Drug Administration (FDA)–approved immunomodulating agents for reducing MS relapses in adults: three preparations of interferon beta (IFNB) and glatiramer acetate (GA).^{12–16} There is also one FDA-approved immunosuppressive medication, mitoxantrone, for patients with worsening MS.¹⁷ Other immunosuppressive agents used empirically for patients with aggressive MS include oral azathioprine, IV immunoglobulins (IVIg), oral methotrexate, oral mycophenolate mofetil, IV cyclophosphamide, and pulses of IV methylprednisolone (MP). Natalizumab, an anti- α 4 integrin, was granted FDA approval

*The first authors contributed equally to this work.

‡Members of the International Pediatric MS Study Group are listed in the Appendix.

From the Department of Pediatrics and Pediatric Neurology (D.P.), Georg-August-University Goettingen, Germany; Multiple Sclerosis Center at UCSF (E.W., D.C.), San Francisco, CA; Department of Pediatric Neurology (B.B.), The Hospital for Sick Children, University of Toronto, Canada; Massachusetts General Hospital for Children (T.C.), Brigham & Women's Hospital, Harvard Medical, Boston; Baird MS Center (B.W.-G.), Jacobs Neurological Institute, Buffalo, NY; and Department of Pediatric Neurology (S.T.), National Pediatric Hospital, Dr. J. P. Garrahan, Buenos Aires, Argentina.

Disclosure: The authors report no conflicts of interest.

Address correspondence and reprint requests to Dr. Emmanuelle Waubant, UCSF MS Center, 350 Parnassus Street, Suite 908, San Francisco, CA 94117; e-mail: Emmanuelle.Waubant@ucsf.edu

S54 Copyright © 2007 by AAN Enterprises, Inc.

Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

Table 1 Available approved therapies

	Interferon beta-1b	Interferon beta-1a	Interferon beta-1a	Random polypeptide (L-glutamic acid, L-lysine, L-alanine, and L-tyrosine)	Mitoxantrone
Production	<i>E coli</i>	Mammalian cells	Mammalian cells	Synthetic	Synthetic
Glycosylated	No	Yes	Yes	NA	NA
Mutation	Met 1 deleted; Cys 17 mutated to a serine	No	No	NA	NA
Administration	SC every other day	IM once a week	SC three times a week	SC every day	IV once every 3 months up to 2 years
Dose per injection	250 µg or 8 MIU	30 µg	44 µg	20 mg	12 mg/m ²
Development of neutralizing antibodies	35%	2–5%	12–24%	No	No
Side effects	Flu-like reaction, LFT increase, skin reaction	Flu-like reaction, LFT increase	Flu-like reaction, LFT increase, skin reaction	Systemic reaction, skin reaction	Infection, cardiotoxicity, early menopause, acute leukemia

LFT = liver function test.

for relapsing forms of MS,^{18–20} but safety concerns arising after three patients developed progressive multifocal leukoencephalopathy (PML) led to its temporary removal from the market. The FDA approved its return in summer 2006. It is expected that the drug will be used as a second line therapy in patients intolerant to or failing on IFNB or GA.

Treatment options and experience in pediatric MS and its variants. *Treatment for relapses.* No therapeutic trial for relapses has yet been conducted in the pediatric MS population. Therefore relapse therapy is based on clinical experience, and extrapolated from studies of acute relapse management in adult MS.

Corticosteroids. In adults, mild relapses or relapses recovering spontaneously do not warrant high dose steroid treatment. Relapses associated with significant neurologic impairment (e.g., interfering with daily function) are usually treated promptly with high doses of IV glucocorticosteroids in order to shorten relapse duration and hasten recovery.^{21–23} High doses of IV methylprednisolone (IVMP) (more than 500 mg/day for at least 3 days in adults) seem superior to lower doses (IV or oral).^{24,25} Recent data suggest that high doses of oral prednisone could substitute for IV pulses in adult MS.²⁶ The typical regimen in adults, 1 g per day for 3 to 5 days administered IV, is generally well tolerated²³ except for occasional insomnia, mood changes, and rare psychosis.

The most frequent side effects of high dose glucocorticosteroids are facial flushing, sleep difficulties, irritability, and increased appetite. In children, growth retardation is an additional concern with prolonged corticotherapy. Although side effects such as high blood pressure and hyperglycemia are rare, es-

pecially in children, treatment with corticosteroids requires careful monitoring of blood pressure, urine glucose, serum potassium, and administration of gastric protection. The risk of side effects increases with prolonged use and total cumulative dose. Corticosteroids used in the doses reviewed are generally well tolerated, even when a short oral taper dose is given.

Plasma exchange. Plasma exchange has been proposed to treat severe relapses in adult patients with MS or NMO when they fail to recover after treatment with high-dose glucocorticosteroids.²⁷ Plasma exchange has also been proposed in children to avoid side effects of frequent pulses of steroids as an alternative treatment for recurrent relapses occurring over a short period. However, the available literature in the pediatric population is restricted to a single case report of a 7-year-old patient with MS with high titers of antinuclear autoantibody.²⁸

IV immunoglobulins. The efficacy of IVIg has never been demonstrated as a preventative or curative relapse therapy in MS or NMO. In adult patients, IVIg therapy (0.4 g/kg daily for 5 days followed by three single infusions monthly for 3 months) was not found to improve visual recovery after optic neuritis,²⁹ nor delay the time to progression in secondary progressive (SP) MS (in a dosage of 1g/kg monthly).³⁰ Although IVIg treatment in combination with high dose glucocorticosteroids does not appear superior to high dose glucocorticosteroids alone to treat relapses,^{31,32} IVIg (in a dosage of 0.4 g/kg daily for 5 days) has been somewhat helpful to children and adults with acute demyelinating attacks who do not improve after high dose MP.^{33–38}

Disease-modifying therapy. Immunomodulatory therapy. Both GA and IFNB are immunomodulators, and decrease relapse rate and MRI activity in

adult patients with relapsing MS.¹²⁻¹⁶ Two IFNB-1a and one IFNB-1b are FDA approved for RRMS (table 1). IM IFNB-1a recently gained a label extension for adults experiencing an initial demyelinating attack, also termed a clinically isolated syndrome (CIS). None of these therapies has been approved for use in the pediatric age group. While there is some reported experience using these therapies in children with MS, efficacy and tolerability data are extremely limited, especially in children under the age of 10 years.

Interferon beta-1b (Betaseron/Betaferon). A retrospective review of safety and tolerability of IFNB-1b in a cohort of 43 children and adolescents with MS was recently reported by an international working group.¹¹ Eight medical centers worldwide with expertise in the care of pediatric MS patients participated in the study. Treatment was initiated at a mean age of 13 years (eight children were less than 11 years old at first injection) for a mean of 30 months. All but two children (both under age 10) received the full adult dose (8 million international units [MIU]), 26 of them after an escalation from an initial dose of 25 to 50% of full dose. No serious or unexpected adverse events (AE) were reported. Most common AE included flu-like symptoms (35%), abnormal liver function test (LFT) (26%), and injection site reactions (21%). There was a trend to higher LFT changes in patients under 10 years of age. This small study and case reports of IFNB-1b treatment in pediatric patients suggest a reasonable short-term safety profile.^{11,39,40}

Long-term efficacy studies are not available; however, a case report of a 7-year-old boy treated with IFNB-1b (4 MIU SC every other day) did not show either a significant clinical relapse or new lesions on follow-up MRIs over a 3-year period.³⁹ In another report, a 15-year-old patient with SPMS treated with IFNB-1b (8 MIU SC three times per week) showed improved neurologic status.⁴⁰

Interferon beta-1a IM (Avonex). Data on tolerability of weekly IM IFNB-1a for treatment of relapsing remitting MS (RRMS) in nine children ≤ 16 years of age was reported in a retrospective study.⁷ Mean duration of therapy was 17 months (range 5 to 36 months). One patient initiated therapy at one third of the dose (10 μg weekly), two patients at one half the dose (15 μg weekly), and six patients at full dose (30 μg weekly); all but the youngest child (8 years old) were escalated to full dose within 1 month. AE included flu-like symptoms (44%), headaches (44%), fever (22%), and injection site soreness (11%). No patient discontinued therapy due to AE.

In another retrospective study, 13 of 16 RRMS patients below 18 years of age were treated with IFNB-1a IM.⁴¹ All but the youngest patient (10 years old) were treated with full dose. IFNB-1a side effects were reported to be mild, and included frequent flu-like symptoms and rare injection site erythema. Treatment was discontinued in 4 cases (31%) because of frequent relapses.

Preliminary results of an Italian multicenter

study (The Immunomodulatory Treatment of Early-onset MS [ITEMS] study) reported 22 patients under the age of 16 years who received IFNB-1a IM (30 μg once a week) for a mean duration of 19.1 months. A reduction of annualized relapse rate from 3.1 (pretreatment) to 0.3 and stable EDSS were reported. However, in the absence of a randomized double blind control design, efficacy data must be considered with caution.⁴²

Interferon beta-1a (Rebif). In a cohort of 46 patients with pediatric MS, 22 μg SC of IFNB-1a treatment was initiated three times weekly. In five additional patients with very active disease, treatment was started at 44 μg three times weekly. The mean age of the participants was 14.6 years (range 8.1 to 17.9 years).¹⁰ The mean duration of therapy was 1.8 years (range 1 month to 4.4 years). Side effects were similar to those described for adult patients: injection site reactions (71%); flu-like symptoms (65%); gastrointestinal symptoms (10%); and blood count (39%) and LFT abnormalities (35%). Two of the 51 patients experienced serious AE. A 12-year-old boy developed a systemic reaction including generalized edema, weakness, fatigue, and mild pleural effusion, 4 weeks after initiating therapy with 22 μg IFNB-1a three times a week. Therapy was discontinued and his symptoms resolved within 2 weeks without any sequelae. In the second case, a 12-year-old boy developed a depressive mood disorder after 13 months of treatment (5 months after increasing the dose to 44 μg three times weekly). Seven other patients discontinued treatment due to various reasons: headache (1), needle phobia (2), inefficacy (1), injection site necrosis (1), nausea (1), and fatigue (1). All but one of the patients could be treated with the adult recommended dose (22 to 44 μg three times weekly). Only a young patient of 8 years of age had to be switched to 22 μg IFNB-1a twice a week injections due to liver enzyme elevation.

In a 6-year prospective, single-center, open-label study, IFNB-1a treatment was initiated in 24 patients of two treatment groups.⁴³ The mean age of study participants was 12.7 years (range 3.8 to 17.9 years). In the first treatment group, IFNB-1a was initiated in eight children with a tentative dose calculated as 33 to 50% of the adult dose of 22 μg three times weekly. After a mean treatment of 29 months (18 to 48 months), the annual relapse rate had increased up to twofold compared to pretreatment values, and a planned dose escalation was subsequently performed. Twenty-three children tolerated the 22 μg tiw dose, 16 of them from the beginning and seven after the dose-escalation phase. The mean exposure to treatment was 44.4 months (range 12 to 89 months). Tolerability was similar to that reported in patients with adult-onset MS. However, two possible serious AE were observed: one patient developed a depressive mood disorder and attempted suicide after 1 year of treatment and another developed treatment-associated polyarthritis after 3 months on IFNB. Therapy was discontinued permanently in

only one of the 24 patients due to concomitant polyarthritis. During the 6-year follow-up, a significant reduction in the relapse rate compared to pretreatment values was observed, but only in the relapsing remitting subgroup receiving IFNB-1a 22 µg tiw.

Additionally, there is one case report of a 7-year-old child with RRMS treated with IFNB-1a SC, who was started at a dose of 2 MIU tiw.⁴⁴ The patient experienced three minor relapses during the first year and a severe exacerbation during the second treatment year. The dose was then increased to 6 MIU (22 µg) tiw. Further follow-up is not available.

None of the aforementioned studies was designed to objectively evaluate treatment efficacy. However, one study reported increased annualized relapse rates (ARR) at doses lower than 22 µg tiw, whereas 22 µg tiw was associated with decreased ARR (1.8 pretreatment compared to 0.14 on drug) and disability compared to baseline.⁴³ In another study, mean ARR decreased on drug (1.9 pretreatment compared to 0.8 on treatment with IFNB-1a SC 22-44 µg tiw).¹⁰ The preliminary results of the ITEMS study including eight patients treated with IFNB-1a 22 µg tiw show a decrease of ARR from 4.1 pretreatment to 0.7 after a mean treatment duration of 48.6 months.⁴²

Glatiramer acetate (Copaxone). GA appeared to be safe and well tolerated in seven children with RRMS at the daily adult dose of 20 mg daily administered SQ for 24 months.⁴⁵ Treatment was initiated in children with a median age of 16.6 years. Reported AE included injection site pain or induration (2/7) and transient systemic reaction (1/7). Although no patient discontinued therapy due to AE, three of seven children discontinued treatment due to frequent relapses and disability progression.

A Web-based survey of 43 patients treated with GA under the age of 18 reported only one patient discontinuing therapy because of side effects.⁹

Preliminary results of the Italian ITEMS study included seven patients treated with GA under the age of 16 years. After a mean treatment duration of 14.7 months, there was a reduced ARR from a baseline of 2.5 to 0.1 on drug and stable EDSS were reported.⁴²

IV immunoglobulins. IVIg has been proposed for pediatric MS patients whose symptoms relapse within days or weeks of discontinuation of steroids.⁹ The reported regimen was 0.4 g/kg initially given daily for 5 days, followed by subsequent IVIg pulse either every other month or every 3 months for a duration ranging from 6 months to 1 year.⁹ An alternative regimen based on a study in adult MS patients⁴⁶ consists of monthly IVIg 1 g/kg/day on two consecutive days and appears to be well tolerated in the pediatric age group (personal communication).

Immunosuppressive therapy. Azathioprine. Oral azathioprine in a dose of 2.5 to 3 mg/kg/day has been used in MS to prevent exacerbations. Data regarding its clinical benefits are available in adult MS patients,⁴⁷⁻⁴⁹ whereas MRI effects have only been studied in small groups of patients.^{50,51} Side effects

include cytopenia, gastrointestinal intolerance, liver toxicity, and skin rashes. The risk to develop cancer on long-term therapy is unclear. The drug remains a reasonable alternative for patients refusing injectables, tolerating poorly IFNB or GA, or not responding to these drugs, but close monitoring of the complete blood count (CBC) and LFTs is recommended.

Management of poor responders. As in adults with MS, some children fail treatment with IFNB or GA, e.g., continue to present acute relapses and progression of disability 6 to 12 months after initiating appropriate regimen of various DMT. There is no accepted definition of MS treatment failure in adults and children. Anecdotal evidence from several groups indicates that a variety of treatments can be used as escalation therapy for children with MS, including the addition of pulse IV steroid treatments to approved DMT, or a switch to chemotherapeutic agents including cyclophosphamide, mitoxantrone, methotrexate, or mycophenolate mofetil. However, there is little experience with these medications in children, and toxicities may limit their use in the pediatric population. The experience with immunosuppressive agents in adults is summarized below. Only a small number of children received between one and three infusions of natalizumab 300 mg before it was pulled off the market in February 2005. Therefore, no conclusion regarding its safety and efficacy in children with MS can be made at this time.

Cyclophosphamide. The efficacy of cyclophosphamide in advanced forms of SPMS is unclear⁵²⁻⁵⁴ although younger adult patients with relapsing MS⁵⁴ or earlier stages of the disease⁵⁵ may derive some benefit. In adults with relapsing disease doing poorly on IFNB, monthly pulses for 6 months have been associated with reduction of disease activity on serial MRI scans compared to monthly IVMP.^{56,57} Pulse cyclophosphamide therapy is started at 800 mg/m² given every 4 weeks. Dose should be titrated for a target WBC nadir of 1,500 to 2,000/mm³ obtained 10 to 12 days after the infusion. IVMP may be given as concomitant treatment.

Short- and long-term safety of cyclophosphamide has not been established in the pediatric population, and common potential side effects may include nausea and vomiting following infusion, risk of infection, transient alopecia, as well as menstrual irregularities and gonadal failure. Oral contraceptives or Lurpron may provide some protection against gonadal failure in girls, and sperm banking should be considered in boys. Fluid loading prior to and after treatment helps prevent hemorrhagic cystitis. The length of treatment varies from a few months to up to 3 years, with the maximum duration limited by the potential risk of hemorrhagic cystitis, bladder cancer, and hematologic malignancies.

Mitoxantrone. A phase III study in worsening adult MS demonstrated that recipients of mitoxantrone compared to placebo experienced significant benefits at 24 months on disability progression,

number of treated relapses, and number of new T2-weighted MRI lesions.¹⁷ Mitoxantrone 12 mg/m² is usually administered IV every 3 months up to 2 years. Above a cumulative dose of 120 mg/m² there is an increased risk of cardiotoxicity. For this reason monitoring ventricular ejection fraction with cardiac echo or multigated angiocardigraphy (MUGA) is now recommended before each infusion. Other side effects include increased risk of infection, early menopause, and very rare therapy-induced leukemia. The experience in children is limited.

Oral methotrexate. Oral methotrexate 7.5 mg per week may slow progression of disability in patients with progressive MS as measured by a composite measure of disability, ambulation, hand function, and MRI.^{58,59} Methotrexate up to 20 mg per week in association with folic acid (1 mg/day) is currently used occasionally in adult patients. Therapy can result in macrocytic anemia that responds well to folate supplement. Other side effects include bone marrow depletion, gastrointestinal disturbances, liver toxicity, and interstitial pneumonitis.

Natalizumab. Natalizumab treatment (300 mg infused monthly) decreases relapse rate by up to 68% and reduces progression of disability by 42% over 2 years.¹⁸⁻²⁰ Natalizumab reduces MRI activity in adult patients with relapsing MS by up to 92% at year 1 and 2.¹⁸⁻²⁰ Safety concerns arising after three patients developed PML led to a suspension of its use in February 2005. In summer 2006, the FDA approved its return on the market as a monotherapy with a special restricted distribution program.

Treatment for progressive forms of MS. There is no approved therapy for primary progressive MS or secondary progressive MS without relapses. The effect of IFNB on pure progression in SPMS is unclear.⁶⁰⁻⁶³ Several phase II and III clinical trials have failed to show a beneficial effect of IFNB-1a, mitoxantrone, IVIg, and GA on progression of disability in PPMS⁶⁴⁻⁶⁶ and SPMS.³⁰ Several drugs are used arbitrarily off-label to attempt preventing progression in patients with SPMS without superimposed exacerbation or PPMS that include pulses of IVMP,⁶⁷ oral methotrexate, and IV cyclophosphamide.

Taking into consideration the rarity of progressive forms of MS in children, it is unlikely that any clinical trials will be feasible in the future. Treatment decisions will therefore have to rely on findings and recommendations in adult MS patients.

Experimental treatments. Recent advances in the treatment of adult MS include the evaluation of new immunomodulatory agents and exploration of neuroprotective agents. A subset of novel MS therapeutics have been previously used for other disorders, both in adults and children, and have an established safety profile. Included in this category are the monoclonal antibodies Daclizumab and rituximab. Although efficacy of some drugs in the adult MS population has been established, strict safety profiles should be established prior to use in pediatric patients.

General recommendations for the treatment of pediatric MS. Relapse therapy. As in adults, relapses associated with significant neurologic impairment warrant high-dose steroid treatment. A typical regimen used by child neurologists is IVMP 20 to 30 mg/kg/day as 1 to 2 hour infusion in the morning for 3 to 5 consecutive days. In view of potential side effects of prolonged steroid treatment in pediatric patients, a subsequent oral taper should be restricted to patients with insufficient resolution of symptoms after IVMP or those patients who experience recurrence of symptoms after IVMP discontinuation. Steroid taper should be kept as short as possible, usually not exceeding 2 to 3 weeks (e.g., prednisone 1 mg/kg/day as a single-morning dose during the first 3 days after IVMP, followed by progressive dose reduction every 2 to 3 days). Although high doses of oral glucocorticosteroids (e.g., MP 10 mg/kg/day as a single morning dose) are an alternative to IVMP treatment, there are no tolerability and efficacy data (apart from personal communications) for children and adolescents with MS. Children with severe relapses not improving after high-dose IVMP pulse or with contraindications to glucocorticosteroids might benefit from a treatment with plasma exchange.

IVIg may be an option for children with contraindications to corticosteroids and mild to moderate attacks, although efficacy has not been formally investigated. IVIg doses up to 1 g/kg/day on 2 consecutive days might be administered.

In children with frequent attacks despite excessive glucocorticosteroid exposure or with steroid dependency (e.g., recurrence of symptoms during or after glucocorticosteroid taper) plasma exchange or IVIg treatment may be considered.

Disease-modifying therapy. Initiation. The International Pediatric MS Study Group agreed that immunomodulatory treatment should be started in children and adolescents with active RR disease (defined clinically or by MRI scans) after MS is diagnosed. More than one exacerbation in a period of 1 to 2 years and new T2-bright lesions or gadolinium-enhancing lesions on repeat brain MRI scans over the same time frame warrant DMT. In patients with a recent clinical exacerbation, any MRI change or enhancement on a follow-up brain MRI 3 to 6 months after the exacerbation would suggest disease activity. In patients whose initial episode includes encephalopathy the use of DMT should be delayed until a second or third attack with more typical MS features has occurred to avoid giving DMT to a child with ADEM or its variants.

Choice of drug. First-line MS therapies include approved drugs for adult MS: IFNB-1a and -1b and GA. The drug should be chosen after discussions with the child and parents that include issues related to compliance, efficacy, and tolerability. In patients with needle phobia or who cannot tolerate DMT a secondary option is azathioprine. Alternatively, IVIg treatment could be considered, especially

for very young children (6 years and younger), given limited knowledge of tolerability of IFNB and GA in this age group.

Dosage. Dose adjustment for IFNB in children younger than 10 years or with a corresponding low body weight might be necessary, especially at initiation of treatment. The initial IFNB dose might be decreased to 25 to 50% of the recommended full dose for adults with MS, followed by a stepwise escalation every 2 to 4 weeks up to full or highest tolerated dose. Use of acetaminophen (15 mg/kg) or ibuprofen (10 mg/kg) at the time of injections and, if necessary, 4 to 6 hours thereafter will lessen frequency and severity of flu-like symptoms during the first months of therapy. GA regimen in children and adolescents is similar to adult regimen. No dose escalation is needed. For second line therapies, such as azathioprine and IVIg, the dosage should be weight adjusted, as done in adult MS.

Follow-up evaluations. Both tolerability and efficacy should be evaluated during follow-up evaluations. Interferon therapy requires laboratory monitoring, especially in the first months after initiation. The authors recommend obtaining CBC with differential, AST, and ALT monthly until the full dosage is reached, every 3 months thereafter, and whenever the patient's well-being is impaired. For patients on azathioprine, CBC every 3 to 6 months will guide decisions regarding the dose and checking AST and ALT every 6 months will monitor liver function.

One approach to evaluate treatment efficacy in an individual patient is to perform neurologic examinations at baseline and at 1, 3, and 6 months, and every 6 months thereafter. In case of a stable disease without attacks, yearly follow-up may be sufficient later on. A repeat brain MRI scan with and without gadolinium should be obtained 6 to 12 months after initiating DMT. This scan should be compared to the baseline scan obtained around the time of treatment initiation. After the first year of therapy in stable patients (no clinical attacks, no new T2-bright areas on treatment at month 12), brain MRI scans can be obtained yearly.

Change of treatment. Change of DMT should be considered in the presence of severe side effects, poor compliance, or in patients who appear to be poor responders.

Compliance. To maximize compliance, young patients and their parents need regular support by frequent follow-up by the clinical team, e.g., clinic visits, phone calls, and a support network. Adolescents are advised to learn to inject themselves and are encouraged to take control of their treatment. As noted elsewhere in this conference report, compliance is generally much better when children have participated in their treatment decisions (see McAlister et al.).^{67b}

Management of poor responders and progressive forms. Addition of IVMP pulses (up to 1 g/day on 3 consecutive days monthly), or switch to mitox-

antrone (up to 12 mg/m² every 3 months), cyclophosphamide (starting at 700 mg/m² monthly), or methotrexate (up to 20 mg weekly), have been used in a few pediatric MS patients who continued to present significant numbers of clinical exacerbations or new MRI lesions while on appropriate regimen of IFNB or GA treated by members of the International Pediatric MS Study Group. Meticulous follow-up protocols are mandatory for all these treatments. Natalizumab therapy is restricted by the FDA to patients over 18 years of age. There are currently too little safety data to consider its use in children.

Treatment options and experience in pediatric patients with MS variants. *Devic disease or neuromyelitis optica.* NMO is the main MS variant in adults. Due to the small number of patients, there has been no randomized clinical trial in this population. Arbitrarily, physicians have used approved or off-label MS drugs. Review of the published literature suggests that IVMP (30 mg/kg/day [under 30 kg of body weight] to 1 g/day [over 30 kg of body weight] for 3 to 5 days) and plasma exchanges for severe exacerbations insufficiently responding to IVMP might help recovery.^{27,68} Long-term therapy with oral azathioprine or IV rituximab may decrease relapse rate.^{69,70} The effect of IFNB and GA is unclear, with only isolated reports.⁷¹ In three children with NMO who were corticosteroid dependent, combined therapy with monthly IV cyclophosphamide and oral methylprednisolone (1 to 2 mg/kg/day) was well tolerated. Combination treatment seemed to reduce relapse rate and improve disability in two children, whereas the third one remained stable.⁷² There are no published data regarding long-term immunosuppressive therapy in children with NMO.

Balo concentric sclerosis. There has been no therapeutic trial for Balo concentric sclerosis due to small numbers of patients. In adults, treatments with corticosteroids,⁷³⁻⁸² mitoxantrone,⁷⁵ immunosuppressants,^{75,80} and plasmapheresis⁷⁹ have been reported to have various efficacy.

To date, only four Balo concentric sclerosis cases with an early onset before the age of 18 years have been published.^{81,83-85} A 4-year-old boy and a 15-year-old girl were treated with high dose corticosteroids and showed subsequent remission for the reported follow-up periods of 5 and 6 months.^{81,84} On the contrary, the effect of corticosteroids in a 13-year-old girl and a 16-year-old boy was questionable and of short duration.^{83,85} Azathioprine treatment did not prevent further attacks in the 16-year-old boy,⁸³ whereas IVIg treatment was followed by a long-lasting remission during a 30-month follow-up in the 13-year-old girl.⁸⁵ In view of the sparse data on therapy for Balo disease no specific treatment recommendations can be made.

Marburg acute MS. Marburg's variant of MS is rare, and there are no reports of pediatric cases in the recent literature. No controlled clinical trials have been done, and there are few reports on thera-

peutic interventions. Treatment with steroids is often unsuccessful.⁸⁶⁻⁹¹ Plasma exchange has been described to be effective in single cases and in some patients in a blinded clinical trial.^{27,90,92} Mitoxantrone was reported to maintain remission after plasma exchanges in two patients.^{90,91} The treatment of pediatric patients with Marburg disease will have to rely on the experience in adult patients in whom plasma exchange and immunosuppressive treatment seem to be beneficial.

Schilder myelinoclastic diffuse sclerosis. Most reported cases of pediatric Schilder disease were treated with high dose and often long course corticosteroids.⁹³⁻¹¹⁰ This treatment was followed by some improvement in the majority of patients. IVIg was used in one patient with questionable effect,¹⁰¹ and in two patients without effect.^{101,106} A 12-year-old boy was treated with cyclophosphamide followed by azathioprine, and was reported to be stable on this regimen,¹⁰³ whereas azathioprine did not prevent progressive decline in a 12-year-old girl.¹⁰¹ Cyclophosphamide treatment in combination with ACTH was followed by complete recovery in another patient who had failed to respond to ACTH alone.¹¹¹ Therapy of pediatric patients with myelinoclastic diffuse sclerosis is based on both anecdotal reports of treatment and recommendations for classic MS.

Symptomatic therapy. There are little published data outlining the frequency of common MS symptoms, such as spasticity, fatigue, bladder dysfunction, and depression, in the pediatric MS population. The DMT available today and presented earlier in this article benefit MS by decreasing the number of relapses and delaying the progression of physical disability. However, these therapies often do not restore already established impairment. Symptomatic therapy plays a role in reducing the physical and emotional consequences of the disease.

Spasticity. The goal of spasticity treatment is to improve mobility, reduce pain, and control painful muscle spasms. In severely affected patients, care involves positioning in order to prevent contractures and pressure sores. The treatments offered to reduce spasticity in children with MS are very similar to methods used in children with severe spastic cerebral palsy. Prior to initiation of any therapeutic program, a careful review of systems is indicated to exclude confounding contributions to spasticity such as urinary tract infection or pain due to musculoskeletal or bone injury. Initial management of spasticity utilizes daily stretching and physical therapy, with particular focus on range-of-motion exercises. If stretching exercises are insufficient, progressive titration of antispastic medication can be considered. Baclofen, a GABA agonist, is the drug of choice for monotherapy. It is particularly useful for reducing the flexor or extensor spasms and increased flexor tone. Starting dose is usually 2.5 mg daily, which can be titrated up gradually to a maximum of 20 to 60 mg/day, based on the response.^{112,113} Tizanidine, a

central alpha-adrenergic agonist, can be considered as monotherapy for patients who do not tolerate baclofen. Tizanidine is started usually at a dose of 1 mg given at bedtime for children under 10 years and can be initiated as 2 mg for children of 10 years or more; maintenance dose is 0.3 to 0.5 mg/kg/day divided four times daily.¹¹⁴ Diazepam and clonazepam also facilitate GABA-mediated synaptic inhibition, and may be of value in selected patients. However, benzodiazepines have significant sedative side effects and exhibit tolerance over time, which often limits their utility. Relatively low evening doses may be effective for nocturnal stiffness and spasms especially in combination with baclofen or tizanidine. Diazepam has been used in the dosage range from 1 to 10 mg per dose; it could be administered up to three to four times per day.¹¹⁵ Clonazepam is rapidly absorbed after oral administration, has a half-life of 18 to 28 hours, and has been used to reduce nighttime muscle spasms. Typical dosage in children is 0.01 to 0.03 mg/kg/day divided BID or TID.¹¹⁶ In cases of medically intractable spasticity or intolerance to oral medications, implantation of a pump placed in the lower abdomen with an intrathecal catheter (intrathecal baclofen, ITB) can deliver continuously baclofen with remarkable efficacy already proven in the adult MS population but also in a significant number of children with cerebral palsy.¹¹⁷ For patients resistant to the previously mentioned antispasticity interventions selective botulinum toxin type A injections can be also considered. Botulinum toxin has successfully relieved severe leg adductor spasticity in some patients, but its high cost, restricted muscle area of benefit, and short lasting effect requiring repeated administrations limit its use. Destructive procedures including surgical neurectomy and rhizotomy are less frequently used since the introduction of the ITB pump, and are of limited applicability.

Fatigue. Many children with MS complain of fatigue. Patients who experience fatigue that is sufficiently severe to interfere with school performance or social activities may benefit from pharmacologic therapy. When evaluating a complaint of fatigue it is important to exclude depression, sleep disturbances, inappropriate dietary interventions, or exhaustion related to physical disability and exposure to heat, which should be diagnosed and appropriately treated.

Pharmacologic management of fatigue in children is based on strategies utilized in the management of adults with MS fatigue. Amantadine 100 to 200 mg qd is the most commonly used antifatigue medication in adult MS.¹¹⁸ Amantadine is an NMDA receptor antagonist with antiviral, neuroprotective, and anti-parkinsonian effects. A recent study showed amantadine to be safe and efficient in treating behavioral changes associated with brain injury in children.¹¹⁹ The dosage used as per pediatric recommendations were as follows: for age 6 to 9 years (weight <40 kg) 5 mg/kg/day up to maximum dose of 150 mg/day; for

Table 2 Medication data

Medication	Dosing information	Class	Beneficial effects	Common side effects	Strategies to reduce side effects
Interferon beta*					
Interferon beta-1b	8 MIU or 250 µg, every other day subcutaneously	Recombinant interferon beta	Exacerbations: Reduced by 30%*	Flu-like symptoms*	Begin with lower than therapeutic dose and gradually escalate*
Interferon beta-1a	30 µg once per week, intramuscular	Recombinant interferon beta	MRI: Reduces the formation of new and enhancing lesions* Disability progression: All DMT likely to have effect in delaying progression of disability on MS-specific rating scales*	Headache, lymphopenia, liver toxicity; potential for spontaneous abortion or teratogenicity unknown*	Premedicate with acetaminophen or NSAIDs*
Interferon beta-1a	22 or 44 µg 3 times per week subcutaneous	Recombinant interferon beta	Fewer patients with clinically isolated syndromes of early MS and MRI abnormalities typical of MS developed clinically definite MS on interferon beta over a 2-year period*	Production of neutralizing antibodies may render agent ineffective in some cases; neutralizing antibodies cross react to all interferon beta forms*	Monitor laboratory parameters (CBC and LFT); use ice and anesthetic cream for painful injection sites; evening injection to minimize side effects during the day; use birth control*
Other DMT					
Glatiramer acetate injections	20 mg daily, subcutaneous	Synthetic polymer	Reduces the number of attacks by 30%; fewer new lesions appear on MRI scan; may have neuroprotective properties	Injection site reactions (mild); "systemic" panic attack-like reaction; lipoatrophy; no neutralizing antibodies; potential for spontaneous abortion or teratogenicity unknown	Use birth control
Mitoxantrone	12 mg/m ² given IV every 3 mo to a lifetime maximum of 144 mg/m ² ; not sure if should be used in combination with the other DMT agents	Cytotoxic; anthracenedione	FDA approved for use in worsening MS; reduces the number of attacks and progression of disability; MRI: Reduces the formation of new and enhancing lesions	At time of the IV: Urine and sclera may turn blue for hours; mild nausea; day 14 after IV: Dramatic transient white blood cell count drop; can worsen concomitant infections; long-term side effects: infertility, premature menopause, cardiac toxicity more likely at doses above recommended, very rare leukemia induced complication, teratogenicity	Check CBC, ESR, and urinalysis with microbiology if needed before each infusion; if chronic neutropenia occurs, reduce the doses or discontinue interferon; check echocardiogram or MUGA scans at baseline and before each infusion; potential benefit of using Lupron every 3 months to preserve fertility in women

*These effects apply to all Interferon beta therapies.

ESR = erythrocyte sedimentation rate.

Continued

age 10 years or older and weight ≥40 kg, 200 mg/day.

If amantadine is not effective, modafinil, a wakefulness-promoting agent, should be considered.^{120,121} The safety of modafinil 50 to 100 mg in the morning in the pediatric population was recently evaluated in a small group of children with spasticity

related to cerebral palsy.¹²² Its effect on fatigue in pediatric MS is unknown. Methylphenidate 10 to 40 mg qd and its extended-release form methylphenidate HCl SR are occasionally used to treat fatigue in adult MS. The potassium channel blockers represent a new approach for treatment of MS symptoms such as weakness and fatigue. This group of drugs, includ-

Table 2 Continued

Symptom/agent/how supplied	Mechanism of action	Common side effects
Spasticity		
Baclofen/10, 20 mg tab	Agonist of GABA-B (inhibitory) receptor	Dizziness, weakness, drowsiness, mental confusion; rapid withdrawal should be avoided
Tizanidine/2, 4 mg tab	Alpha-2 receptor agonist: acts on polysynaptic reflex arc	Sedation, liver function abnormalities, orthostatic hypotension
Diazepam/2, 5, 10 mg tab	Enhance the GABAergic transmission	Sedation, addiction
Clonazepam/0.5, 1, 2 mg tab	Enhance the GABAergic transmission	Sedation, addiction
Dantrolene/25, 50, 100 mg	Direct action on skeletal muscle (decreasing the calcium release from ER)	Weakness, hepatotoxicity, fatigue
Fatigue		
Amantadine/100 mg	N-methyl-D aspartate antagonist	Nausea, unusual dreams, peripheral edema, livedo reticularis
Methylphenidate HCl/10, 20 mg; methylphenidate HCl SR/20 mg	Central nervous stimulant	Insomnia, agitation
Modafinil/100 mg	Alpha-1 adrenergic agonist, noradrenalin reuptake inhibitor	Headache, insomnia, restlessness
Bladder disturbance		
Oxybutinin/5 mg, and in the sustained release formulation 10 mg, 15 mg	Anticholinergic agent	Constipation, dry mouth, increased risk of urinary retention
Tolterodine/2 mg, Detrol LA 4 mg	Anticholinergic agent	Constipation, dry mouth, increased risk of urinary retention
Hyoscyamine/0.125 or the sustained release formulation 0.375 mg	Anticholinergic agent	Constipation, dry mouth, increased risk of urinary retention
TCA/10, 25, 50, 75 mg	Tricyclic antidepressant with anticholinergic properties	Constipation, dry mouth, increased risk of urinary retention, confusion, orthostatic hypotension

DMT = disease-modifying therapy; MS = multiple sclerosis; NSAID = nonsteroidal anti-inflammatory drug; CBC = complete blood count; LFT = liver function tests; FDA = Food and Drug Administration; ESR = erythrocyte sedimentation rate.

ing 4-aminopyridine and 3, 4-diaminopyridine, has been tested in MS clinical trials, showing benefit in strength and ambulation.¹²³ The side effect of most concern has been seizures, and thus any child with a history of seizures should not be offered these medications.

Tremor and ataxia. Cerebellar tremor and ataxia are among the most disabling neurologic symptoms of MS and respond poorly to most therapies. Fortunately, although ataxia and tremor are common features of acute MS relapse, in the authors' experience most children show spontaneous improvement of these symptoms. Occupational and physical therapy can be helpful in providing adaptive equipment (e.g., wrist weights, Rollator, peripheral cooling) for safe walking and other daily activities. In our experience, clonazepam is the most effective

treatment for MS intention tremor (table 2). Another treatment option is primidone (initiated as 25 to 50 mg hs and increased every 2 to 3 weeks up to 250 mg if tolerated).¹²⁴ In adults, stimulation of the ventral intermediate thalamic nucleus (deep brain stimulation, DBS) is a promising new technique that has been demonstrated to be effective in parkinsonian, essential, and intention tremor. Preliminary results in adult MS patients have demonstrated considerable success in tremor control. The procedure is being recommended only for carefully selected patients with relatively stable disease, in whom upper extremity tremor is the most disabling symptom.¹²⁵ There is no published experience in children with MS.

Paroxysmal symptoms. Paroxysmal symptoms occur abruptly during exacerbations of MS, spread

within seconds, and last for seconds to minutes with no enduring deficit. They may present as motor tonic spasms or sensory paresthesias, occur repeatedly, are promoted by hyperventilation, and can be painful. Treatment with IVMP (500 mg to 1000 mg/day) for 3 to 5 days may be sufficient to treat the relapse but sometimes symptoms last several weeks and require short-term symptomatic treatment. Acetazolamide can be initiated at the full dose (250 mg BID–TID in adults) with the advantage of not being sedative contrarily to anticonvulsants. Carbamazepine is also useful even in usually subtherapeutic anticonvulsant dosages.

Cognitive impairment. Cognitive impairment occurs in up to 50% of MS adult patients even in the first stages of the disease and recent pediatric MS studies have called attention to similar deficits.^{126,127} Recent studies in adult MS suggest functional improvement using donepezil therapy.^{128,129} At this point, a more in-depth understanding of the scope, severity, and consequences of cognitive impairment in pediatric MS patients is urgently required before pharmacologic intervention can be considered.

Urologic and bowel disorders. Disruption of bladder function is a common and distressing problem in adult MS patients, but appears to be relatively infrequent in children with MS. Neurogenic disorders of the bladder include detrusor hyperreflexia with urge incontinence, frequently associated with sphincter dyssynergia and areflexia with urinary retention. A more exact evaluation is obtained using videourodynamic studies. Early recognition of abnormal urodynamic parameters can prevent serious urologic complications.

Urinary tract infections are frequent in adult MS patients (40 to 60%) and should be the first concern at the time of initial inquiry about bladder disturbances. Detrusor hyperreflexia (without significant post-voided urine residual [PVR], e.g. PVR below 100 mL) usually responds to anticholinergic agents. The most commonly used are oxybutynin, tolterodine, and hyoscyamine. A recent study that evaluated the effectiveness and tolerability of tolterodine (0.1 mg/kg/day for patients under 5 years and 2 mg/day for older children, divided into two doses) and oxybutynin (0.4 mg/kg/day, divided into three doses) in children with detrusor instability showed that although the reductions in the urge urinary incontinence episodes were similar with tolterodine and oxybutynin, tolterodine showed significantly better tolerability.¹³⁰ Anticholinergic treatment overdose can result in urinary retention. Detrusor-sphincter dyssynergia (with significant urine residual, PVR above 100 to 150 mL) responds to combination of anticholinergic agents with intermittent straight catheterization (ISC). Severe nocturia unresponsive to evening fluid restriction, anticholinergic medication, and ISC might respond to desmopressin acetate nasal spray 0.1 to 0.2 mL (10 to 20 µg) given at bedtime.

Similar to bladder dysfunction, bowel dysfunction is rare in children with MS. Constipation is more common than bowel incontinence, but some patients experience an alternating pattern. Maintaining a good fluid intake, scheduled defecation 30 to 60 minutes after eating, bulk-forming agents (bran and psyllium), and stool softeners such as docusate sodium are often helpful.

Summary. Given the goal of inhibiting disease progression and disability, the Study Group suggests that children with MS be treated with the DMTs approved for use in adults. Given the limited experience and the lack of approved drugs in the pediatric population, the group strongly recommends that treatment is initiated and supervised by practitioners experienced in pediatric MS. In view of the potential severe long-term consequences of pediatric MS, treatment should not be delayed into adulthood but started early in the disease course.

Appendix

The International Pediatric MS Study Group: Lauren Krupp, MD (chair), Brenda L. Banwell, MD, Anita Belman, MD, Dorothee Chabas, MD, PhD, Tanuja Chitnis, MD, Peter Dunne, MD, Andrew Goodman, MD, Jin S. Hahn, MD, Deborah P. Hertz, MPH, Nancy J. Holland, EdD, RN, MSCN, Douglas Jeffery, MD, PhD, William MacAllister, PhD, Raul Mandler, MD, Maria Milazzo, RN, MS, CPNP, Jayne Ness, MD, PhD, Jorge Oksenberg, PhD, Trena L. Pelham, MD, Daniela Pohl, MD, PhD, Kottil Rammohan, MD, Mary R. Rensel, MD, Christel Renoux, MD, Dessa Sadovnick, PhD, Steven Robert Schwid, MD, Silvia Tenenbaum, MD, Cristina Toporas, Emmanuelle Waubant, MD, PhD, Bianca Weinstock-Guttman, MD.

References

1. Boiko A, Vorobeychik G, Paty D, Devonshire V, Sadovnick D. UBC MS Clinic Neurologists. Early onset multiple sclerosis. A longitudinal study. *Neurology* 2002;59:1006–1010.
2. Simone IL, Carrara D, Tortorella C, et al. Course and prognosis in early-onset MS. Comparison with adult-onset forms. *Neurology* 2002; 59:1922–1928.
3. Jacobs LD, Beck RW, Simon JH, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. *N Engl J Med* 2000;343:898–904.
4. Comi G, Filippi M, Barkhof F, et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomized study. *Lancet* 2001;357:1576–1582.
5. PRISMS Study Group and the University of British Columbia MS/MRI Analysis Group. PRISMS-4: Long-term efficacy of interferon-beta-1a in relapsing MS. *Neurology* 2001;56:1628–1636.
6. Hanefeld F. Multiple sclerosis in childhood. *Curr Opin Neurol Neurosurg* 1992;5:359–363.
7. Waubant E, Hieptas J, Stewart T, et al. Interferon beta-1a in children with multiple sclerosis is well tolerated. *Neuropediatrics* 2001;32:211–213.
8. Banwell B. Treatment of children and adolescents with multiple sclerosis. *Exp Rev Neurother* 2005;5:391–401.
9. Krupp LB, Macallister WS. Treatment of pediatric multiple sclerosis. *Curr Treat Options Neurol* 2005;7:191–199.
10. Pohl D, Rostasy K, Gärtner J, Hanefeld F. Treatment of early onset multiple sclerosis with subcutaneous interferon beta-1a. *Neurology* 2005;65:888–890.
11. Banwell B, Reeder AT, Krupp L, et al. Safety and tolerability of interferon beta-1b in pediatric multiple sclerosis. *Neurology* 2006;66:472–476.
12. The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993;43:655–661.
13. Johnson KP and the Copolymer 1 Multiple Sclerosis Study Group. Copolymer 1 reduces relapse rate and improves disability in relapsing remitting multiple sclerosis: results of a phase III multicenter, double blind, placebo-controlled trial. *Neurology* 1995;45:1268–1276.
14. Jacobs LD, Cookfair D, Rudick R, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Ann Neurol* 1996;39:285–294.

15. PRISMS study group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing remitting multiple sclerosis. *Lancet* 1998;352:1498–1504.
16. Comi G, Filippi M, Wolinsky JS, and the European/Canadian Glatiramer Acetate Study Group. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effect of glatiramer acetate on magnetic resonance imaging-measured disease activity and burden in patients with relapsing multiple sclerosis. *Ann Neurol* 2001; 49:290–297.
17. 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.
18. Miller DH, Khan OA, Sheremata WA, et al. A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2003;348:15–23.
19. Polman C, O'Connor P, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006;354:899–910.
20. Rudick R, Stuart W, Calabresi P, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med* 2006;354:911–923.
21. Goodin DS, Frohman EM, Garmany GP, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology* 2002;58: 169–178.
22. Andersson PB, Goodkin DE. Glucocorticosteroid therapy for multiple sclerosis: a critical review. *J Neurol Sci* 1998;160:16–25.
23. Brusaferrri F, Candelise L. Steroids for multiple sclerosis and optic neuritis: a meta-analysis of randomized controlled clinical trials. *J Neurol* 2000;247:435–442.
24. Beck RW. The optic neuritis treatment trial: three-year follow-up results. *Arch Ophthalmol* 1995;113:136–137.
25. Oliveri RL, Valentino P, Russo C, et al. Randomized trial comparing two different high doses of methylprednisolone in MS: a clinical and MRI study. *Neurology* 1998;50:1833–1836.
26. Miller DM, Weinstock-Guttman B, Bethoux F, et al. A meta-analysis of methylprednisolone in recovery from multiple sclerosis exacerbations. *Mult Scler* 2000;6:267–273.
27. Weinstock-Guttman B, O'Brien PC, Petterson TM, et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. *Ann Neurol* 1999;46:878–886.
28. Takahashi I, Sawaishi Y, Takeda O, Enoki M, Takada G. Childhood multiple sclerosis treated with plasmapheresis. *Pediatr Neurol* 1997; 17:83–87.
29. Noseworthy JH, O'Brien PC, Petterson TM, et al. A randomized trial of intravenous immunoglobulin in inflammatory demyelinating optic neuritis. *Neurology* 2001;56:1514–1522.
30. Hommes OR, Sorensen PS, Fazekas F, et al. Intravenous immunoglobulin in secondary progressive multiple sclerosis: randomised placebo-controlled trial. *Lancet* 2004;364:1149–1156.
31. Visser LH, Beekman R, Tijssen CC, et al. A randomized, double-blind, placebo-controlled pilot study of i.v. immune globulins in combination with i.v. methylprednisolone in the treatment of relapses in patients with MS. *Mult Scler* 2004;10:89–91.
32. Sorensen PS, Haas J, Sellebjerg F, Olsson T, Ravnborg M. IV immunoglobulins as add-on treatment to methylprednisolone for acute relapses in MS. *Neurology* 2004;63:2028–2033.
33. Finsterer J, Grass R, Stollberger C, Mamoli B. Immunoglobulins in acute, parainfectious, disseminated encephalo-myelitis. *Clin Neuroparmacol* 1998;21:258–261.
34. Nishikawa M, Ichiyama T, Hayashi T, Ouchi K, Furukawa S. Intravenous immunoglobulin therapy in acute disseminated encephalomyelitis. *Pediatr Neurol* 1999;21:583–586.
35. Apak RA, Anlar B, Saatci I. A case of relapsing acute disseminated encephalomyelitis with high dose corticosteroid treatment. *Brain Dev* 1999;21:279–282.
36. Pradhan S, Gupta RP, Shashank S, Pandey N. Intravenous immunoglobulin therapy in acute disseminated encephalomyelitis. *J Neurol Sci* 1999;165:56–61.
37. Sahlas DJ, Miller SP, Guerin M, Veilleux M, Francis G. Treatment of acute disseminated encephalomyelitis with intravenous immunoglobulin. *Neurology* 2000;54:1370–1372.
38. Murthy SN, Faden HS, Cohen ME, Bakshi R. Acute disseminated encephalomyelitis in children. *Pediatrics* 2002;110:e21.
39. Adams A, Tyor W, Holden K. Interferon beta-1b and childhood multiple sclerosis. *Pediatr Neurol* 1999;21:481–483.
40. Schilling S, Haertel C, Sperner J. Follow-up of interferon beta-1b treatment in a 15-year-old patient with secondary progressive multiple sclerosis. *Neuropediatrics* 2002;33:A31.
41. Mikaeloff Y, Moreau T, Debouverie M, et al. Interferon β treatment in patients with childhood-onset multiple sclerosis. *J Pediatr* 2001;139: 443–446.
42. Ghezzi A, Ruggieri M, Trojano M, Filippi M, and the ITEMS Study Group. Italian studies on early-onset multiple sclerosis: the present and the future. *Neurol Sci* 2004; 24:S346–S349.
43. Tenenbaum SN, Segura MJ. Interferon beta-1a treatment in childhood and juvenile-onset multiple sclerosis. *Neurology* 2006;67:511–513.
44. Etheridge LJ, Beverley DW, Ferrie C, McManus E. The use of interferon beta in relapsing-remitting multiple sclerosis. *Arch Dis Child* 2004;89:789–791.
45. 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;34:120–126.
46. Sorensen PS, Wanschler B, Jensen CV, et al. Intravenous immunoglobulin G reduces MRI activity in relapsing multiple sclerosis. *Neurology* 1998;50:1273–1281.
47. Goodkin DE, Baily RC, Teetzen ML, Hertsgaard D, Beatty WW. The efficacy of azathioprine in relapsing-remitting multiple sclerosis. *Neurology* 1991;41:20–25.
48. Yudkin PL, Ellison GW, Ghezzi A, et al. Overview of azathioprine treatment in multiple sclerosis. *Lancet* 1991;338:1051–1055.
49. Palace J, Rothwell P. New treatments and azathioprine in multiple sclerosis. *Lancet* 1997;350:261.
50. Cavazzuti M, Merelli E, Tassone G, Mavilla L. Lesion load quantification in serial MR of early relapsing multiple sclerosis patients in azathioprine treatment. A retrospective study. *Eur Neurol* 1997;38: 284–290.
51. Massacesi L, Parigi A, Barilaro A, et al. Efficacy of azathioprine on multiple sclerosis new brain lesions evaluated using magnetic resonance imaging. *Arch Neurol* 2005;62:1843–1847.
52. Hauser SL, Dawson DM, Lehrich JR, et al. Intensive immunosuppression in progressive multiple sclerosis: a randomized, three-arm study of high-dose intravenous cyclophosphamide, plasma exchange, and ACTH. *N Engl J Med* 1983;308:173–180.
53. Canadian Cooperative Multiple Sclerosis Study Group. The Canadian co-operative trial of cyclophosphamide and plasma exchange in progressive multiple sclerosis. *Lancet* 1991;337:441–446.
54. Weiner H, Mackin G, Orav E, et al. Intermittent cyclophosphamide pulse therapy in progressive multiple sclerosis: final report of the Northeast Cooperative Multiple Sclerosis Treatment Group. *Neurology* 1993;43:910–918.
55. Hohol MJ, Olek MJ, Orav EJ, et al. Treatment of progressive multiple sclerosis with pulse cyclophosphamide/methylprednisolone: response to therapy is linked to the duration of progressive disease. *Mult Scler* 1999;5:403–409.
56. Gobbi MI, Smith ME, Richert ND, Frank JA, McFarland HF. Effect of open label pulse cyclophosphamide therapy on MRI measures of disease activity in five patients with refractory relapsing-remitting multiple sclerosis. *J Neuroimmunol* 1999;99:142–149.
57. Smith DR, Weinstock-Guttman B, Cohen J, et al. Randomized trial of pulse cyclophosphamide in IFNB resistant active MS. *Neurology* 2002; 64:55 (suppl 3).
58. Goodkin DE, Rudick RA, VanderBrug Medendorp S. Low-dose (7.5 mg) oral methotrexate reduces the rate of progression in chronic progressive multiple sclerosis. *Ann Neurol* 1995;37:30–40.
59. Goodkin DE, Rudick RA, VanderBrug Medendorp S, Daughtry MM, Van Dyke CD. Low-dose oral methotrexate in chronic progressive multiple sclerosis: analyses of serial MRI's. *Neurology* 1996;47:1153–1157.
60. Kappos L, Polman C, Pozzilli C, et al. Final analysis of the European multicenter trial on IFNbeta-1b in secondary-progressive MS. *Neurology* 2001;57:1969–1975.
61. Li DK, Zhao GJ, Paty DW. University of British Columbia MS/MRI Analysis Research Group. The SPECTRIMS Study Group. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: MRI results. *Neurology* 2001;56:1505–1513.
62. Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-beta-1a in MS (SPECTRIMS) Study Group. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: clinical results. *Neurology* 2001;56:1496–1504.
63. Cohen JA, Cutter GR, Fischer JS, et al. Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. *Neurology* 2002; 59:679–687.
64. Leary SM, Miller DH, Stevenson VL, Brex PA, Chard DT, Thompson AJ. Interferon beta-1a in primary progressive MS. An exploratory, randomized, controlled trial. *Neurology* 2003;60:44–51.
65. Kita M, Cohen J, Fox B. A phase II trial of mitoxantrone in patients with primary progressive multiple sclerosis. *Neurology* 2004;62(suppl 5):A99.
66. Wolinsky J, Pardo L, Stark Y, et al. Effect of glatiramer acetate on primary progressive multiple sclerosis: initial analysis of the completed PROMiSe trial. *Neurology* 2004;62(suppl 5):A97.
67. Goodkin DE, Kinkel RP, Weinstock-Guttman B, et al. A phase II study of i.v. methylprednisolone in secondary-progressive multiple sclerosis. *Neurology* 1998;51:239–245.
- 67b. Macallister WS, Boyd JR, Holland NJ, et al., for the International Pediatric MS Study Group. The psychosocial consequences of pediatric multiple sclerosis. *Neurology* 2007;68(suppl 2):S66–S69.
68. Keegan M, Pineda AA, McClelland RL, Darby CH, Rodriguez M, Weinstock-Guttman B. Plasma exchange for severe attacks of CNS demyelination: predictors of response. *Neurology* 2002;58:143–146.

69. Mandler RN, Ahmed W, Dencoff JE. Devic's neuromyelitis optica: a prospective study of seven patients treated with prednisone and azathioprine. *Neurology* 1998;51:1219-1220.
70. Cree BAC, Lamb S, Morgan K, Chen A, Waubant E, Genain C. An open label study of the effects of rituximab in neuromyelitis optica. *Neurology* 2005;64:1270-1272.
71. Wingerchuk DM. Neuromyelitis optica: current concepts. *Front Biosci* 2004;9:834-840.
72. Tenembaum S, Segura MJ, Astorino F, Rios V, Katsicas MM, Russo R. Neuromyelitis optica in children: clinical course and preliminary results of immunosuppressive treatment. *Neurology* 2003; 60(suppl 1): A480.
73. Moore GR, Neumann PE, Suzuki K, et al. Baló's concentric sclerosis: new observations on lesion development. *Ann Neurol* 1985;17:604-611.
74. Spiegel M, Krüger H, Hofmann E, Kappos L. MRI study of Baló's concentric sclerosis before and after immunosuppressive therapy. *J Neurol* 1989;236:487-488.
75. Hanemann CO, Kleinschmidt A, Reifenberger G, Freund HJ, Seitz RJ. Baló's concentric sclerosis followed by MRI and positron emission tomography. *Neuroradiology* 1993;35:578-580.
76. Gharagozloo AM, Poe LB, Collins GH. Antemortem diagnosis of Baló concentric sclerosis: correlative MR imaging and pathologic features. *Radiology* 1994;191:817-819.
77. Korte JH, Bom EP, Vos LD, Breuer TJM, Wondergem JHM. Baló concentric sclerosis: MR diagnosis. *Am J Neuroradiol* 1994;15:1284-1285.
78. Kim MO, Lee SA, Choi CG, Huh JR, Lee MC. Baló's concentric sclerosis: a clinical case study of brain MRI, biopsy, and proton magnetic resonance spectroscopic findings. *J Neurol Neurosurg Psychiatry* 1997; 62:655-658.
79. Sekijima Y, Tokuda T, Hashimoto T, et al. Serial magnetic resonance imaging (MRI) study of a patient with Baló's concentric sclerosis treated with immunoadsorption plasmapheresis. *Mult Scler* 1997;2: 291-294.
80. Moore GRW, Berry K, Oger JFF, et al. Baló's concentric sclerosis: surviving normal myelin in a patient with a relapsing-remitting clinical course. *Mult Scler* 2001;7:375-382.
81. Karaarslan E, Altintas A, Senol U, et al. Baló's concentric sclerosis: clinical and radiologic features of five cases. *Am J Neuroradiol* 2001; 22:1362-1367.
82. Kastrup O, Stude P, Limmroth V. Baló's concentric sclerosis. Evolution of active demyelination demonstrated by serial contrast-enhanced MRI. *J Neurol* 2002;249:811-814.
83. Louboutin JP, Elie B. Treatment of Baló's concentric sclerosis with immunosuppressive drugs followed by multimodality evoked potentials and MRI. *Muscle Nerve* 1995;18:1478-1480.
84. Murakami Y, Matsui T, Shimizu T, et al. Baló's concentric sclerosis in a 4-year-old Japanese infant. *Brain Dev* 1998;20:250-252.
85. Pohl D, Rostasy K, Krone K, Hanefeld F. Baló's concentric sclerosis associated with primary human herpesvirus 6 infection. *J Neurol Neurosurg Psychiatry* 2005;76:1723-1725.
86. Lebow S, Anderson DC, Matri A, Larson D. Acute multiple sclerosis with contrast-enhancing plaques. *Arch Neurol* 1978;35:435-439.
87. Mendez MF, Pogacar S. Malignant monophasic multiple sclerosis or "Marburg's disease." *Neurology* 1988;38:1153-1155.
88. Johnson MD, Lavin P, Whetsell WO Jr. Fulminant monophasic multiple sclerosis, Marburg's type. *J Neurol Neurosurg Psychiatry* 1990; 53:918-921.
89. Wood DD, Bilbao JM, O'Connors P, Moscarello MA. Acute multiple sclerosis (Marburg type) is associated with developmentally immature myelin basic protein. *Ann Neurol* 1996;40:18-24.
90. Jacquerye P, Ossemann M, Laloux P, Dive A, DeCoene B. Acute fulminant multiple sclerosis and plasma exchange. *Eur Neurol* 1999;41: 174-175.
91. Jeffery DR, Lefkowitz DS, Crittenden JP. Treatment of Marburg variant multiple sclerosis with mitoxantrone. *J Neuroimaging* 2004;14:58-62.
92. Rodriguez M, Karnes WE, Bartleson JD, Pineda AA. Plasmapheresis in acute episodes of fulminant CNS inflammatory demyelination. *Neurology* 1993;43:1100-1104.
93. Poser CM, Goutieres F, Carpentier MA, Aicardi J. Schilder's myelinoclastic diffuse sclerosis. *Pediatrics* 1986;77:107-112.
94. Mehler MF, Rabinowich L. Inflammatory myelinoclastic diffuse sclerosis. *Ann Neurol* 1988;23:413-415.
95. Rodesch G, Avni EF, Parizel P, et al. Schilder's disease: neuroradiologic findings. *J Neuroradiol* 1988;15:386-393.
96. Lana-Peixoto MA, dos Santos EC. Schilder's myelinoclastic diffuse sclerosis. *J Clin Neuroophthalmol* 1989;9:236-240.
97. Barth PG, Derix MM, de Krom MC, Valk J, Theunissen PM. Schilder's diffuse sclerosis: case study with three years' follow-up and neuroimaging. *Neuropediatrics* 1989;20:230-233.
98. Ehlen F, Poremba M, Grodd W, Opitz H, Roggendorf W, Dichgans J. Myelinoclastic diffuse sclerosis (Schilder's disease): cliniconeuroradiologic correlations. *Neurology* 1991;41:589-591.
99. Affi AK, Bell WE, Menezes AH, Moore SA. Myelinoclastic diffuse sclerosis (Schilder's disease): report of a case and review of the literature. *J Child Neurol* 1994;9:398-403.
100. Stachniak JB, Mickle JP, Ellis T, Quisling R, Rojiani AM. Myelinoclastic diffuse sclerosis presenting as a mass lesion in a child with Turner's syndrome. *Pediatr Neurosurg* 1995;22:266-269.
101. Garell PC, Menezes AH, Baumbach G, et al. Presentation, management and follow-up of Schilder's disease. *Pediatr Neurosurg* 1998;29: 86-91.
102. Pretorius ML, Loock DB, Ravenscroft A, Schoeman JF. Demyelinating disease of Schilder type in three young South African children: dramatic response to corticosteroids. *J Child Neurol* 1998;13:197-201.
103. Leuzzi V, Lyon G, Cilio MR, et al. Childhood demyelinating diseases with a prolonged remitting course and their relation to Schilder's disease: report of two cases. *J Neurol Neurosurg Psychiatry* 1999;66: 407-408.
104. Fitzgerald MJ, Coleman LT. Recurrent myelinoclastic diffuse sclerosis: a case report of a child with Schilder's variant of multiple sclerosis. *Pediatr Radiol* 2000;30:861-865.
105. Affi AK, Follett KA, Greenlee J, Scott WE, Moore SA. Optic neuritis: a novel presentation of Schilder's disease. *J Child Neurol* 2001;16:693-696.
106. Poppe M, Bruck W, Hahn G, et al. Fulminant course in a case of diffuse myelinoclastic encephalitis: a case report. *Neuropediatrics* 2001;32:41-44.
107. Nejat F, Eftekhari B. Decompressive aspiration in myelinoclastic diffuse sclerosis or Schilder disease. *J Neurosurg* 2002;97:1447-1449.
108. Obara S, Takeshima H, Awa R, et al. Tumefactive myelinoclastic diffuse sclerosis. *Neurol Med Chir* 2003;43:563-566.
109. Kurul S, Cakmakci H, Dirik E, Kovanlikaya A. Schilder's disease: case study with serial neuroimaging. *J Child Neurol* 2003;18:58-61.
110. Garrido C, Levy-Gomes A, Teixeira J, Temudo T. Schilder's disease: two new cases and a review of the literature. *Rev Neurol* 2004;39:734-738.
111. Konkol RJ, Bousounis D, Kuban KC. Schilder's disease: additional aspects and a therapeutic option. *Neuropediatrics* 1987;18:149-152.
112. Goldstein EM. Spasticity management: an overview. *J Child Neurol* 2001;16:16-23.
113. Krach LE. Pharmacotherapy of spasticity: oral medications and intrathecal baclofen. *J Child Neurol* 2001;16:31-36.
114. Wagstaff AJ, Bryson HM, Tizanidine. A review of its pharmacology, clinical efficacy and tolerability in the management of spasticity associated with cerebral and spinal disorders. *Drugs* 1997;53:435-452.
115. Patel DR, Soyode O. Pharmacologic interventions for reducing spasticity in cerebral palsy. *Ind J Pediatr* 2005;72:869-872.
116. Matthews DJ, Wilson P. Cerebral palsy. In: Molnar GE, Alexander MA, eds. *Pediatric rehabilitation*, 3rd ed. Philadelphia: Hanley & Belfus, 1999:193-218.
117. Gooch JL, Oberg WA, Grams B, Ward LA, Walker ML. Care provider assessment of intrathecal baclofen in children. *Dev Med Child Neurol* 2004;46:548-552.
118. Krupp LB, Coyle PK, Doscher C, et al. Fatigue therapy in multiple sclerosis: results of a double-blind, randomized, parallel trial of amantadine, pemoline, and placebo. *Neurology* 1995;45:1956-1961.
119. Beers SR, Skold A, Dixon CE, Adelson PD. Neurobehavioral effects of amantadine after pediatric traumatic brain injury: a preliminary report. *J Head Trauma Rehabil* 2005;20:450-463.
120. Rammohan KW, Rosenberg JH, Lynn DJ, Blumenfeld AM, Nagaraja HN. Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. *J Neurol Neurosurg Psychiatry* 2002;72:179-183.
121. Stankoff B, Waubant E, Confavreux C, et al. Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study. *Neurology* 2005;64:1139-1143.
122. Hurst DL, Lajara-Nanson W. Use of modafinil in spastic cerebral palsy. *J Child Neurol* 2002;17:169-172.
123. Schwid SR, Petrie MD, McDermott MP, et al. Quantitative assessment of sustained-release 4-aminopyridine for symptomatic treatment of multiple sclerosis. *Neurology* 1997;48:817-821.
124. Anouti A, Koller WC. Tremor disorders. Diagnosis and management. *West J Med* 1995;162:510-513.
125. Schuder M, Sernas TJ, Karimi R. Thalamic stimulation in patients with multiple sclerosis: long-term follow-up. *Stereotact Funct Neurosurg* 2003;80:48-55.
126. Mac Allister WS, Belman AL, Milazzo M, et al. Cognitive functioning in children and adolescents with multiple sclerosis. *Neurology* 2005; 64:1422-1425.
127. Banwell BL, Anderson PE. The cognitive burden of multiple sclerosis in children. *Neurology* 2005;64:891-894.
128. Greene YM, Tariot PN, Wishart H, et al. A 12-week, open trial of donepezil hydrochloride in patients with multiple sclerosis and associated cognitive impairments. *J Clin Psychopharmacol* 2000;20:350-356.
129. Krupp LB, Christodoulou C, Melville P, Scherl WF, MacAllister WS, Elkins LE. Donepezil improved memory in multiple sclerosis in a randomized clinical trial. *Neurology* 2004;63:1579-1585.
130. Kilic N, Balkan E, Akgoz S. Comparison of the effectiveness and side-effects of tolterodine and oxybutynin in children with detrusor instability. *Int J Urol* 2006;13:105-108.