

# Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis

Multiple Sclerosis Journal  
0(0) 1–12  
© The Author(s) 2012  
Reprints and permission:  
sagepub.co.uk/journalsPermissions.nav  
DOI: 10.1177/1352458511430704  
msj.sagepub.com  


**T Chitnis<sup>1</sup>, S Tenenbaum<sup>2</sup>, B Banwell<sup>3</sup>, L Krupp<sup>4</sup>, D Pohl<sup>5</sup>, K Rostasy<sup>6</sup>, E A Yeh<sup>7</sup>, O Bykova<sup>8</sup>, E Wassmer<sup>9</sup>, M Tardieu<sup>10</sup>, A Kornberg<sup>11</sup>, A Ghezzi<sup>12</sup> and for the International Pediatric Multiple Sclerosis Study Group**

## Abstract

New therapies are being evaluated by clinical trials and, if efficacious, introduced for the treatment of adult MS. The role of these new and existing agents in the management of pediatric MS has yet to be defined. Pediatric investigation plans are now required by the Food and Drug Administration and European Medicines Agency for approval of new biological agents, providing an important opportunity to gather much-needed data for clinicians caring for children and adolescents with MS. However, challenges include the small number of patients, and the need for efficient yet comprehensive study designs incorporating factors necessary to inform the clinical care of children with MS. The elected Steering committee of the International Pediatric MS Study Group (IPMSSG) conducted a structured review of existing data on the disease-modifying therapies in pediatric MS and developed a consensus statement, which was further modified by the IPMSSG general membership, using an online survey tool. Fifty-one IPMSSG members from 21 countries responded to the survey, and 50 approved the final statement. Consensus recommendations regarding use of existing first- and second-line therapies, as well as a proposed definition for inadequate treatment response, are presented. Recommendations for the use and evaluation of emerging therapies (currently in phase III clinical trials or recently approved for adult MS) are discussed. The IPMSSG endorses the inclusion of pediatric MS patients in trials evaluating appropriate new and emerging therapies. Mechanisms for conducting high-impact, multicenter studies, including long-term follow-up in pediatric MS, are required to ensure that all MS patients, irrespective of age, benefit from advances in MS therapeutics.

## Keywords

disease-modifying therapies, multiple sclerosis

Date received: 5th October 2011; revised: 29th October 2011; accepted: 30th October 2011

## Introduction

Approximately 3–5% of multiple sclerosis (MS) patients experience their first MS attack during childhood.<sup>1–5</sup> First- and second-line MS disease-modifying treatments are used in children and adolescents.<sup>6–9</sup> However, most medication use is off-label since therapies shown in clinical adult trials to have efficacy and which have been approved for adult MS have not been formally evaluated by clinical trials in children. In some regions of the world, regulatory approval restricts administration of MS disease-modifying therapies to patients 12 years and older.

With the recent approval of the first oral disease-modifying medication (fingolimod in the US, Europe, and Russia in 2010, and Canada and Australia in 2011), and the likely approval of new intravenous, injectable, and oral MS therapies in the next few years, practitioners caring for

<sup>1</sup>Partners Pediatric Multiple Sclerosis Center, Massachusetts General Hospital, Boston, MA, USA.

<sup>2</sup>National Pediatric Hospital, Dr J P Garrahan, Buenos Aires, Argentina.

<sup>3</sup>The Hospital for Sick Children, University of Toronto, Canada.

<sup>4</sup>Stony Brook University Medical Center, Stony Brook, NY, USA.

<sup>5</sup>Children's Hospital of Eastern Ontario, University of Ottawa, Canada.

<sup>6</sup>Department of Pediatrics IV, Division of Pediatric Neurology and Inborn Errors of Metabolism, Innsbruck Medical University, Innsbruck, Austria.

<sup>7</sup>Department of Neurology, SUNY Buffalo, Buffalo, NY, USA.

<sup>8</sup>Moscow Pediatric Psychoneurological Hospital, Moscow, Russia.

<sup>9</sup>Birmingham Children's Hospital, Birmingham, UK.

<sup>10</sup>Assistance Publique-Hôpitaux de Paris, Hôpital Bicêtre and Université Paris-Sud, Paris, France.

<sup>11</sup>Royal Children's Hospital, Melbourne, Australia.

<sup>12</sup>Multiple Sclerosis Study Center, Hospital of Gallarate, Gallarate, Italy.

## Corresponding author:

Tanuja Chitnis, MD, Partners Pediatric Multiple Sclerosis Center, Massachusetts General Hospital, ACC-708, 55 Fruit Street, Boston, MA 02114 USA  
Email: tchitnis@partners.org

children and adolescents with MS will increasingly face challenges in recommending the most appropriate therapy, particularly given the lack of therapeutic studies in pediatric MS. Fortunately, this issue has been addressed by the American (FDA) and European (EMA) regulatory agencies, which have recently implemented guidelines for the inclusion of pediatric investigation plans for new pharmacologic agents, with the aim of ensuring safe and appropriate access to promising new therapies for children and adolescents.

Therapeutic studies in pediatric MS must take into account the small numbers of patients available for inclusion, which will have significant impact on study power and design. Pediatric therapeutic trials also face the challenges of surrogate decision-making by parents, potentially more stringent ethical constraints, and a far more limited experience with clinical trials relative to adult trial research. In this milieu, the International Pediatric MS Study Group (IPMSSG) has developed a consensus statement specifically with regard to the current use and further evaluation of existing as well as new MS disease-modifying therapies recently approved, or currently in phase III clinical trials in adult MS.

## Methods

An initial outline for this consensus statement was developed by the elected Steering Committee of the IPMSSG (TC, ST, BB, LK, DP, KR, OB, EW, MT, AK, AG) and invited speakers (EAY, GC). The IPMSSG is a global network of adult and pediatric neurologists, basic scientists, clinicians, and representatives of MS societies and other relevant professional organizations, whose unifying vision is to optimize worldwide healthcare, education, and research in pediatric MS and other acquired inflammatory demyelinating disorders of the central nervous system. Additional details about the membership and policies of the IPMSSG are available on its website ([www.ipmssg.org](http://www.ipmssg.org)). Attendees reviewed topics including pediatric MS treatment and management, and published data on emerging MS therapies using Medline or regional medical search engines, in languages including English, Spanish, French, German, and Russian. Reviewed studies were rated according to level of therapeutic evidence (class I – IV), in line with AAN guidelines.<sup>10</sup> Compiled data were presented to this group at a face-to-face meeting on September 26, 2010 funded by the MS International Federation, National MS Society, and Canadian MS Society. A working document was developed by the Steering Committee and reviewed by external reviewers (AT and CP), and the general membership of the IPMSSG using online tools (SurveyMonkey). Feedback was provided by reviewers, and only items in which consensus was reached were included in this document. All IPMSSG members who gave their final

consent for submission of this manuscript are listed in the appendix.

## Results

### General considerations

- This consensus statement refers only to relapsing forms of pediatric MS as defined by Krupp et al.<sup>11</sup>
- This statement does not provide guidelines for primary progressive MS in children, since this condition is extremely rare and research in this area is lacking.
- This consensus statement applies to all patients under the age of 18 years.

### Disease course of pediatric multiple sclerosis

Although pediatric-onset MS closely resembles adult-onset relapsing–remitting MS (RRMS), several features of the disease in children should be noted. Children experience 2–3 times more frequent relapses than adults early in the disease course, with annualized relapse rates of 1.12–2.76 compared with 0.3–1.78 seen in adults.<sup>12</sup> Approximately one-third of children demonstrate evidence of significant cognitive deficits early in the disease course.<sup>13,14</sup> In addition, a longitudinal study found that 75% of patients demonstrated worsening cognitive function on follow-up testing at 2 years.<sup>15</sup> Accrual of locomotor disability, as measured by the Expanded Disability Status Scale score, takes longer from first attack in pediatric-onset as compared with adult-onset MS patients.<sup>2,16–18</sup> However, pediatric-onset MS patients will reach disability milestones at younger ages than their adult-onset counterparts. Comparative MRI studies have shown a higher T2 lesion burden in children with MS compared with adults,<sup>19,20</sup> supporting the concept that MS in children is more inflammatory than that in adults.

### First-line disease-modifying therapies

*Beta-interferon and glatiramer acetate use in pediatric multiple sclerosis.* Beta-interferons and glatiramer acetate have been used in adult MS for over 15 years, as first-line therapy, and are widely used in the pediatric MS population on the basis of class I evidence in adult MS. There are a number of class IV published studies outlining short-term safety profiles as well as efficacy outcomes in pediatric MS patients. (reviewed in Supplementary Tables 1a–d, Waubant et al.,<sup>21</sup> Mikaeloff et al.,<sup>22</sup> Ghezzi et al.,<sup>23,24,25</sup> Pohl et al.,<sup>26</sup> Tenenbaum et al.,<sup>27</sup> Banwell et al.,<sup>28</sup> Kornek et al.<sup>29</sup>) A survey of 42 US physicians found that all used first-line therapies for children with MS.<sup>30</sup> Other publications have documented general use of first-line therapies,<sup>30–32</sup> supporting the view that use of first-line therapies in pediatric

**Supplementary Table 1 (a).** Summary of first-line pediatric MS therapies (IFN  $\beta$ -1a 30 mcg IM once per week [selected studies]).

IFN $\beta$ -1a IM	Waubant et al. <sup>21</sup>	Mikaeloff et al. <sup>22</sup>	Ghezzi et al. <sup>23</sup>	Ghezzi et al. 2007 <sup>24</sup>	Ghezzi et al. <sup>25</sup>
Study design	Retrospective	Retrospective	Retrospective multicenter	Prospective multicenter	Prospective multicenter
Rating of therapeutic study	IV	IV	IV	III	III
Number of children (n)	9	13	38	52	77
Age at treatment onset (mean, years)	12.7	15.5	12.1	Not reported	11.4
Duration of treatment (mean, months)	17	12	23	43	54
Starting dose	1/3 dose 1/9 1/2 dose 2/9 Full dose 6/9	1/2 dose 1/13 Full dose 12/13	Full dose	Full dose	Full dose (within 1–2 months)
Final (full) dose	8/9	12/13	38/38	52/52	77/77
Annualized relapse rate (before/after treatment)	Not reported	Not reported	2.4/ 0.4	2.1/0.3	2.5/ 0.4
Discontinuation	2/9 (22%) Frequent attacks	4/13 (31%) Frequent attacks	6/38 (16%) 4 frequent attacks 2 persistent flu-like symptoms	19/52 (37%) 9 lack of efficacy 4 adverse events 6 other reasons	20 (26%) lost to follow-up or stopped treatment 23 (30%) shifted to other treatments
<b>Adverse events</b>					
Flu-like symptoms	4/9	11/13	19/38 (50%)	33%	19 (25%)
Myalgia	2/9	3/13	6/38 (18%)	21%	7 (9%)
Injection site reaction	1/9	2/13	5/38 (12%)	4%	5 (6.5%)
Elevation of liver enzymes	Not reported	1/13	2/38 (4.5%)	2 (4%)	4 (5%)

**Supplementary Table 1 (b).** Summary of first-line pediatric MS therapies (IFN  $\beta$ -1a 22 mcg SC or 44 mcg [selected studies]).

IFN $\beta$ -1a 22 mcg or 44 mcg	Pohl et al. <sup>26</sup>	Tenembaum et al. <sup>27</sup>	Ghezzi et al. <sup>25</sup>
Study design	Retrospective	Prospective single center	Prospective multicenter
Rating of therapeutic study	IV	III	III
Number of children (n)	51	24	36
Age at treatment onset (mean, years)	14.6	12.7	12.6
Duration of treatment (mean, months)	22	44.4	59.9
Starting dose	22 mcg = 46/51 44 mcg = 5/51	33–50% dose = 8/24 22 mcg = 16/24	Full dose (within 1–2 months)
Final (full) dose	22 mcg = 24 44 mcg = 27	22 mcg = 23/24	22 mcg = 36
ARR (mean before/after treatment)	1.9/0.8	1.7/0.04	3.2/1.0
Relapse free (n, %)	21 (41)	19 (79)	Not reported
<b>Adverse events</b>			
Flu-like symptoms (%)	65	58	7.7
Menstrual disorder (menorrhagia, %)	0	11 (1/9 ♀)	Not reported
Injection site reaction (%)	71	75	18
Elevation of liver enzymes (%)	35	33	Not reported
Blood count abnormalities (%)	39	8	8
<b>Serious adverse events</b>			
Systemic reaction (n)	1 (aged 12 years)	0	Not reported
Depressive mood disorder (n)	1 (aged 12 years)	1 (aged 14 years)	Not reported
Juvenile chronic arthritis-like illness (n)	0	1 (aged 15 years) (DRBI*0404, DQBI*0301 alleles)	Not reported

**Supplementary Table 1(c).** Summary of first-line pediatric MS therapies (IFN  $\beta$ -1b 250 mcg SC [selected study]).

IFN $\beta$ -1b	Banwell et al. <sup>28</sup>	Banwell et al. <sup>28</sup>
Study design	Retrospective multicenter	
Rating of therapeutic study	IV	
Number of children (n)	43	
Age at treatment onset (mean, years)	13	
Duration of treatment (mean, months)	29.2 $\pm$ 22.3	
Starting dose	25–50% of full dose = 33/43 Full dose (250 mcg) = 15/43	
Final (full) dose 250 mcg SC, every other day	41/43	
<b>Adverse events</b>	<b>Children aged <math>\leq</math> 10 years n = 8</b>	<b>Children aged &gt; 10 years n = 35</b>
Flu-like symptoms (n, %)	2 (25)	13 (37)
Asthenia (n, %)	0	1 (3)
Injection site reaction (n, %)	2 (25)	7 (20)
Elevation of liver enzymes > twofold ULN (n, %)	5 (62.5)	3/30 (10)
<b>Discontinued IFN beta-1b</b>	3	22
Injection pain	0	1
Lack of efficacy	0	5
Other causes	3	16

**Supplementary Table 1(d).** Summary of first-line pediatric MS therapies (glatiramer acetate [selected studies]).

Glatiramer acetate	Kornek et al. <sup>29</sup>	Ghezzi et al. <sup>24</sup>	Ghezzi et al. <sup>25</sup>
Study design	Prospective single center	Prospective multicenter	Prospective multicenter
Rating of therapeutic study	III	III	III
Number of children (n)	7	9	14
Age at treatment onset (mean, years)	16.6	13.2	13.1
Duration of treatment (mean, months)	24	33	64
Starting dose	20 mg daily	20 mg daily	20 mg daily
Final (full) dose	7	9	14
Annualized relapse rate (before/after treatment)	Not reported	2.8/0.25	3.1/0.2
<b>Adverse events</b>			
Transient systemic reaction (n, %)	1 (14)	1 (11)	1 (7)
Injection site reaction (n, %)	4 (57)	Not reported	2 (14.2)

MS (where available) is generally accepted as the standard of care.<sup>30–33</sup> Based on these findings, the IPMSSG recommends that all pediatric patients with MS, as defined by Krupp et al.,<sup>11</sup> should be considered for treatment with either a beta-interferon or glatiramer acetate as first-line therapy.

**Beta-interferon and glatiramer acetate use in clinically isolated syndrome.** There are no published data regarding the use of beta-interferon or glatiramer acetate in children with a first demyelinating attack or “clinically isolated syndrome.” Several groups have found that the presence of well-defined lesions, periventricular and corpus callosum lesions, and T1 black holes on MRI obtained at the time of a first attack have a high sensitivity in predicting further relapses leading

to confirmation of MS.<sup>34–37</sup> It is therefore recognized that children manifesting with a first demyelinating attack with these certain clinical and MRI features, which are associated with a high risk of MS, may benefit from prompt initiation of therapy in order to delay or modify the severity of subsequent relapses.

**Titration and dosing.** There are only two published studies of varied doses of beta-interferons in children with MS.<sup>26,27</sup> There have been no studies of titration schedules in pediatric MS. However, studies in adults have not demonstrated a clear weight or body mass index (BMI) relationship with beta-interferon dosing. We recommend that children be titrated to full dose as tolerated, using adult titration schedules for guidance.

Glatiramer acetate in adults is commenced at full dose. Although there have been no studies of dose-finding and titration in children with MS, clinical practice is to initiate at full dose.

**Safety monitoring.** Retrospective studies have demonstrated that the short-term safety profile of beta-interferons and glatiramer acetate in children is similar to that observed in adults.<sup>21,24–28</sup> Laboratory testing for these agents should be conducted as per product information guidelines. The long-term safety profile is an important area of further study, since despite reassuring safety data in adults, long-term safety data including effects on growth and puberty in children do not exist.

### ***Inadequate treatment response in pediatric multiple sclerosis***

There is a lack of global consensus on the definition of inadequate treatment response for adult MS. Published consensus statements and studies in adult MS have suggested that 1–2 annual relapses or no improvement in relapse frequency can be considered as treatment failures,<sup>38–40</sup> or the occurrence of two or more T2 brain MRI lesions or one or more Gd<sup>+</sup> lesions during the first year of treatment.<sup>40</sup> In a retrospective study of 258 pediatric MS patients, 44% switched to another first- or second-line therapy over a 3-year period because of an inadequate treatment response as determined by treating physicians.<sup>42</sup> These findings emphasize the high frequency of perceived inadequate treatment response in MS and underscore the importance of determining a precise definition for inadequate treatment response in pediatric MS through prospective studies. Until such studies can be performed, we propose the following working definition, which requires evaluation for sensitivity and specificity and may be modified as more information becomes available.

Proposed working definition for inadequate treatment response in pediatric MS:

- Minimum time on full-dose therapy 6 months\*
- AND
- Fully compliant on treatment
- AND at least one of the following:
- Increase or no reduction in relapse rate, or new T2 or contrast enhancing lesions on MRI from pre-treatment period
- $\geq$  Two confirmed relapses (clinical or MRI relapses) within a 12-month period or less

\*Mechanism of action, pharmacokinetics, and pharmacodynamics of specific agents should be taken into consideration.

Defining inadequate treatment response should be individualized to specific patients, and may take into account

additional features such as relapse symptoms, location, and severity. Poor recovery from relapse and disease progression may also be considered in defining inadequate treatment response; however, it is acknowledged that further studies are required to adequately define both in children. Rapid cognitive decline should also be taken into account. There are currently few data regarding subclinical (MRI) disease evolution in pediatric MS and treatment effects, and this is an important area for further study. Decisions regarding switching treatment should be balanced with potential adverse effects of subsequent treatment.

### ***Therapeutic options for inadequate treatment response***

In cases of inadequate treatment response, options for switching treatments include changing between first-line therapies (beta-interferon and glatiramer acetate) or switching to a second-line agent described below. Studies in adult patients treated with interferon have demonstrated that the development of sustained serum positivity for neutralizing antibodies to beta-interferon is associated with failure to respond to interferon therapy.<sup>43</sup> Although there are no formal studies of neutralizing antibodies to beta-interferons in pediatric MS, the biological nature of the assay suggests that the presence of neutralizing antibodies in children with relapses while on interferon therapy may be considered as an indication for switching to a different non-interferon therapy.

Combination use of a baseline disease-modifying therapy and add-on of monthly intravenous high-dose steroids, such as methylprednisolone, can be used for short periods such as 6–12 months in patients with inadequate response to treatment. Complications of prolonged steroid use including osteoporosis, hypertension, hyperglycemia, cataracts, and increased risk of infection must be taken into account when considering combination therapy.

Some patients are candidates for second-line therapy as suggested from small cohort studies of natalizumab<sup>41,44,45</sup> and cyclophosphamide<sup>46</sup> therapy in pediatric MS (discussed in more detail below). However, larger studies including dosing, pharmacokinetic and pharmacodynamics monitoring, as well as long-term safety and efficacy measures are required to clearly define the roles of these and other second-line agents in pediatric MS. Decisions to switch to a specific agent will depend on patient characteristics and a collaborative informed decision made by the physician, family, and patient, weighing the risks and benefits of each specific treatment.

### ***Emerging multiple sclerosis therapies***

Several new treatments are in the late stages of development or early approval in the adult MS population. Some

of these agents could have an important role in the management of pediatric MS, and require further evaluation in this population. At present, there is a lack of clarity regarding which therapies should be evaluated in pediatric MS, and how to optimally design studies. The IPMSSG has agreed on the following guidelines regarding recommendations for use and evaluation of investigational agents in pediatric MS.

### **Recommendations regarding the general use and evaluation of investigational agents in pediatric multiple sclerosis**

The IPMSSG supports the view that appropriate emerging therapies should be evaluated in pediatric MS, with the hope that new efficacious and reasonably safe treatments will be identified, and proposes the following approaches listed in Table 1. Specific study designs should be guided by the available information regarding the mechanism of action of the drug, efficacy data, side effects, and tolerability profile, as well as dose-related effects.

See Table 1: Recommendations for the evaluation of investigational agents in pediatric MS.

### **Patient populations**

All children with a diagnosis of MS, as defined by Krupp et al.,<sup>11</sup> should be considered for inclusion in clinical trials of pediatric MS. It is recognized that there may be some differences in the clinical<sup>47</sup> or biological presentation<sup>48,49</sup> of prepubertal children and postpubertal adolescents with MS. In addition, there are some important differences in the pediatric immune profile detailed elsewhere,<sup>50,51</sup> which may be relevant to the mechanisms of action of some

agents. However, unless there is a clear rationale to exclude patients of a specific age group because of safety or efficacy concerns, both children and adolescents should be considered for inclusion in investigational MS studies. The risks of frequent MRIs potentially requiring anesthesia or other monitoring interventions should be considered when developing clinical trial designs that include very young children.

### **Pharmacokinetic and pharmacodynamic issues**

Absorption, distribution, metabolism, and elimination (ADME) of drugs can be affected by age-related factors, independent of BMI, and are relevant to the dosing of certain drugs for pediatric MS patients. The FDA statement, "Guidance for Industry: General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products," classifies pediatric patients into neonates (birth–1 month), infant (1 month–2 years), children (2–12 years), and adolescents (12–16 years).<sup>52</sup> Levels of hepatic metabolizing enzymes may be significantly different in neonates and infants compared with adults. However, there are certain ADME differences in the child and adolescent categories, which comprise the vast majority of pediatric MS patients. Activity of the phase I hepatic enzyme FMO<sup>53</sup> can differ significantly in children compared with adults. Differences in CYP1A2 levels according to sex and Tanner staging have been observed.<sup>54</sup> There is limited information on phase II hepatic enzymes in children and adolescents. The renal glomerular filtration rate reaches adult values by 1 year of age,<sup>55</sup> and therefore is less of a concern in pediatric MS patients. The pharmacokinetics of a particular agent and potential differences in children and adolescents

**Table 1.** Recommendations for the evaluation of investigational agents in pediatric MS.

1. Exposure of pediatric MS patients to new therapeutic agents should occur in the context of carefully designed clinical trials. Off-label use of emerging therapies is generally discouraged, with the hope that pediatric MS patients may be enrolled in well-controlled, robust clinical trials evaluating appropriate agents.
2. New and emerging therapies of high potency and potentially serious or life-threatening toxicity should have a reasonable period of post hoc safety information from adults before consideration for study in the pediatric age group. Re-examination for pediatric indications emphasizing safety and tolerability in this age group is then reasonable.
3. For new and emerging therapies with proven efficacy demonstrated by phase III trials in adults and favorable side effect profiles, appropriate studies in pediatric MS should be conducted to evaluate safety and efficacy.
4. Pediatric MS studies could be developed in tandem with phase III adult RRMS trials only if available safety data demonstrate a favorable risk/benefit ratio, information exists on drugs with the same or similar mechanism of action, or if sufficient safety data in children treated with the drug for other disorders already exist.
5. 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.
6. In situations where use of a specific therapy is restricted to very small patient populations (such as patients with severe or refractory MS), a clinical trial may not be feasible. In this situation, a prospective registry of all treated patients should be employed to capture both short-term and long-term safety and tolerability.
7. All pediatric MS clinical trials should include a long-term prospective registry to capture information about long-term safety and development and fertility parameters.

compared with adults must be taken into account when considering use and dosing of specific MS therapies.

Pharmacodynamic studies in pediatric MS patients are recommended if biological markers related to drug action are available. Efficacy of the drug may be influenced by differences in either the developing immune system, discussed below, or in the developing nervous system.

### *Developing immune system: points for consideration*

Developmental differences in the immune system between children and adults may affect immunotherapy mechanism of action or efficacy. The immune system of healthy children and adolescents differs in some aspects from adults.<sup>50</sup> Thymic involution starts in puberty and leads to a relative decrease in circulating T cells in adults.<sup>56</sup> There is a significant reduction in repertoire diversity of B and T cells in the elderly compared with the young.<sup>57–60</sup> The ratio of naïve:memory T cells is highest in childhood and decreases with age.<sup>61</sup> The proportion of HLA-DR+ CD4+ T cells is highest in the 6–10-year-old group and declines in puberty.<sup>62</sup> NK cells are lowest in the neonatal period and increase steadily with age.<sup>62</sup> The proportion of CD4+CD25hi is high in neonates, decreases in the 6–10 years age group, and increases again in pubertal and adult groups.<sup>62</sup> Some of these differences may be relevant to the mechanism of action and efficacy of some immunotherapies, and should be taken into account when considering use in children and adolescents.

### *Safety and tolerability studies*

Studies in pediatric MS should assess safety parameters identified in adult MS studies throughout the duration of the study period. In addition, a protocol to follow safety parameters long-term in pediatric MS patients should be developed. When relevant, safety studies of pediatric-age animals should also be included in early new drug development or as post hoc analyses when appropriate. Studies in pediatric MS should assess tolerability and adherence, and identify factors that affect both parameters. Development of strategies to enhance tolerability and adherence of agents in pediatric MS is encouraged.

### *Efficacy outcome measures*

The ultimate goal of disease-modifying therapy (DMT) in MS is to prevent relapses and permanent physical and cognitive deficits. Choice of efficacy outcome measures of specific therapies may depend on the mechanism of action of the agent, effects in adults, and potential unique effects in children. The higher relapse rates in children relative to adults during the first 3 years of disease<sup>12</sup> should be taken into account when choosing efficacy outcomes. Since

cognitive dysfunction is prominent in pediatric MS,<sup>13–15</sup> it is strongly recommended that the effects of treatment on cognitive function be included as outcome measures. Additional potential treatment outcomes are MRI measures of lesion accrual and cerebral atrophy; however, lack of controlled, longitudinal data make estimation of sample sizes challenging.

### *Effects on development and fertility*

All studies should assess physical development including height, weight, and BMI over the study duration and post-study long-term. Also, effects on endocrinological maturity, including onset and frequency of menses should be assessed. Adequate birth control in postmenarcheal girls should be practiced and routine pregnancy tests performed while on treatment. The effect or potential effects on fertility must be evaluated when considering drugs for study. For agents for which this is a major concern, strategies to preserve sperm or gonadal function should be strongly considered.

### *Vaccination efficacy*

Since children require frequent vaccinations, vaccine safety and efficacy while on specific MS disease-modifying treatment needs to be evaluated in pediatric populations. In particular, guidelines regarding the administration of live versus inactivated or peptide vaccine while on specific therapy need to be established.

### *Long-term studies*

Long-term studies of safety, tolerability, and compliance in pediatric MS patients are recommended for all medications being used or evaluated, since children might be exposed to MS therapies for the majority of their lives. In particular, effects on fertility, and risk of severe and opportunistic infections and malignancy need to be assessed. Mechanisms to follow safety and adherence in patients long-term should be developed in all pediatric MS studies. Ideally, a shared prospective data resource that permits long-term shared outcome data would facilitate more evidence-based recommendations and lead to earlier identification of any safety issues.

### *Recommendations regarding specific second-line and emerging therapies*

*Natalizumab*: Natalizumab (Tysabri®) is approved for the treatment of relapsing forms of adult MS based on class I studies,<sup>63,64</sup> in the US for RRMS, and in Europe for patients with inadequate response to first-line immunotherapy or severe, rapidly evolving RRMS. Available open-label data (class IV) in children with MS suggest that natalizumab, in

most cases, reduces clinical and MRI relapses.<sup>41,45</sup> However, the risk profile must be balanced with potential benefits and these factors should be comprehensively discussed with the family and patient. The most significant adverse effect is an approximately 1:1000 risk of progressive multifocal leukoencephalopathy (PML) observed in adult patients. An assay to assess exposure to JC virus through the presence of serum antibodies is currently being investigated, and may stratify patients into low- and high-risk groups for PML.<sup>65</sup> Two large population-based studies have demonstrated that children and adolescents have lower rates of JC virus infection than adults;<sup>66,67</sup> however, specific JC virus infection rates are unknown in children and adolescents with MS. Enhanced understanding of the risk of PML during primary JC virus acquisition is required, since this may be particularly relevant to the pediatric MS population. Additional questions that need to be addressed regarding natalizumab include optimal dosing regimens and pharmacokinetic studies in pediatric MS.

**Mitoxantrone:** Mitoxantrone (Novantrone<sup>®</sup>) is approved for the treatment of worsening adult RRMS on the basis of class I studies. Cardiotoxicity has been reported as a severe adverse event and there is also an increased risk of leukemia, which may present years after cessation of therapy. Two recent studies demonstrated high rates of leukemia: 1:333 in a cohort of 5472 patients<sup>68</sup> and 1:107 patients in a cohort of 3220 patients.<sup>69</sup> One study of four pediatric patients followed between 3.8 and 18 years found no long-term adverse events.<sup>70</sup> Because of its risk profile, the IPMSSG discourages the use of mitoxantrone in children.

**Cyclophosphamide:** Cyclophosphamide (Cytosan<sup>®</sup>) is not approved for the treatment of MS, although pulse cyclophosphamide has been shown to reduce disease activity in adult MS in class I studies.<sup>71,72</sup> Adults 40 years or under were better responders than those over 40 years.<sup>72</sup> In a retrospective class IV study of 17 children and adolescents with inadequate treatment response to other immunosuppressive-immunomodulatory treatments, cyclophosphamide treatment reduced relapse rate and halted disease progression in the majority of cases.<sup>46</sup> There has been considerable experience with cyclophosphamide in other pediatric autoimmune diseases<sup>73-75</sup> as well as in pediatric leukemia, and this experience can inform management of children with MS including information regarding dosing and side effects. Patients should be monitored for the risk of severe adverse events including infections, amenorrhea, sterility, bladder cancer, and other secondary malignancies.

**Rituximab:** Rituximab (Rituxan<sup>®</sup>) is not approved for the treatment of MS, but beneficial effects have been reported in a class I phase II study in adult RRMS, showing significant reduction of brain lesions and clinical relapses.<sup>76</sup> Reduction in relapse rate has been reported in an adolescent

treated with rituximab, without significant side effects.<sup>77</sup> Nevertheless, cases of PML have been reported in patients with systemic lupus erythematosus (SLE) and other autoimmune diseases treated with rituximab.<sup>78</sup> The possible relationship of rituximab treatment and the development of PML and other severe infections raises particular concerns regarding its use in children. Studies are required to evaluate optimal dosing, safety, and efficacy of rituximab in pediatric MS.

**Fingolimod:** Fingolimod (Gilenya<sup>™</sup>) was approved for adult MS in the US, Europe, and Russia in 2010 and in Australia and Canada in 2011. No information regarding safety, tolerability, and optimal dosing in children currently exists. A pediatric investigation plan for fingolimod in pediatric MS patients has recently been approved by the EMA, but details of the study design are in process, and enrolment of pediatric MS patients has not yet commenced. Specific concerns regarding fingolimod use in pediatric MS are its effects on thymic T-cell maturation and egress,<sup>79</sup> as well as infection risk.

**Cladribine:** This drug was approved in Australia and Russia in 2010. However, in 2011, it was voluntarily withdrawn from the market and is therefore no longer available as a treatment for MS.

For the following drugs phase III trials are ongoing or are not yet published.

**Teriflunomide, BG00012, Laquinimod, Alemtuzumab, Daclizumab, Ocrelizumab:** in the opinion of the IPMSSG there is currently insufficient information in adult MS patients to make specific recommendations about use or studies of these agents in pediatric MS. Studies in pediatric MS could be considered once complete phase III safety and efficacy data are available.

## Conclusions

Children and adolescents generally experience an inflammatory form of MS, and are at risk for serious cognitive and physical sequelae. Reports and studies demonstrate that beta-interferon and glatiramer acetate are widely used in pediatric MS, and are generally accepted as the standard of care. Evidence from adult-onset MS strongly supports the favorable impact of prompt initiation of therapy on disease outcomes. The IPMSSG endorses access for all pediatric MS patients to currently approved forms of beta-interferon and glatiramer acetate. New therapeutic agents may offer improved tolerability and efficacy profiles. Conduct of robust clinical studies in pediatric MS patients evaluating appropriate new and emerging therapies will be challenging, but has the high likelihood of providing high-quality, evidence-based care of these children. This, in turn will ensure that all MS patients, irrespective of age, benefit from advances in MS therapeutics.

## Acknowledgements

We would like to thank Professor Giancarlo Comi for valuable input during the inaugural meeting. We would like to thank Professor Alan Thompson and Professor Christopher Polman for critical reviewing of this manuscript. The meeting of the IPMSSG Steering committee and invited speakers on September 26, 2010 was funded by the MS International Federation, National MS Society, and the Canadian MS Society.

## Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## Conflict of interest statement

None declared.

## References

- Duquette P, Murray TJ, Pleines J, Ebers GC, Sadovnick D, Weldon P, et al. Multiple sclerosis in childhood: clinical profile in 125 patients. *J Pediatr* 1987; 111: 359–363.
- Boiko A, Vorobeychik G, Paty D, Devonshire V and Sadovnick D. Early onset multiple sclerosis: a longitudinal study. *Neurology* 2002; 59: 1006–1010.
- Ghezzi A, Deplano V, Faroni J, Grasso MG, Liguori M, Marrosu G, et al. Multiple sclerosis in childhood: clinical features of 149 cases. *Mult Scler* 1997; 3: 43–46.
- Sindern E, Haas J, Stark E and Wurster U. Early onset MS under the age of 16: clinical and paraclinical features. *Acta Neurol Scand* 1992; 86: 280–284.
- Chitnis T, Glanz B, Jaffin S and Healy B. Demographics of pediatric-onset multiple sclerosis in an MS center population from the Northeastern United States. *Mult Scler* (Houndmills) 2009; 15: 627–631.
- Pohl D, Waubant E, Banwell B, Chabas D, Chitnis T, Weinstock-Guttman B, et al. Treatment of pediatric multiple sclerosis and variants. *Neurology* 2007; 68 (Suppl. 2): S54–S65.
- Yeh EA, Chitnis T, Krupp L, Ness J, Chabas D, Kuntz N, et al. Pediatric multiple sclerosis. *Nat Rev Neurol* 2009; 5: 621–631.
- Kuntz NL, Chabas D, Weinstock-Guttman B, Chitnis T, Yeh EA, Krupp L, et al. Treatment of multiple sclerosis in children and adolescents. *Expert Opin Pharmacother* 2010; 11: 505–520.
- Ghezzi A, Banwell B, Boyko A, Amato MP, Anlar B, Blinkenberg M, et al. The management of multiple sclerosis in children: a European view. *Mult Scler* (Houndmills) 2010; 16: 1258–1267.
- Goodin DS, Frohman EM, Garmany GP, Jr., Halper J, Likosky WH, Lublin FD, 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.
- Krupp LB, Banwell B and Tenenbaum S. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. *Neurology* 2007; 68(Suppl. 2): S7–S12.
- Gorman MP, Healy BC, Polgar-Turcsanyi M and Chitnis T. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. *Arch Neurol* 2009; 66: 54–59.
- Amato MP, Goretti B, Ghezzi A, Lori S, Zipoli V, Portaccio E, et al. Cognitive and psychosocial features of childhood and juvenile MS. *Neurology* 2008; 70: 1891–1897.
- MacAllister WS, Belman AL, Milazzo M, Weisbrot DM, Christodoulou C, Scherl WF, et al. Cognitive functioning in children and adolescents with multiple sclerosis. *Neurology* 2005; 64: 1422–1425.
- Amato MP, Goretti B, Ghezzi A, Lori S, Zipoli V, Muiola L, et al. Cognitive and psychosocial features in childhood and juvenile MS: two-year follow-up. *Neurology* 2010; 75: 1134–1140.
- Renoux C, Vukusic S, Mikaeloff Y, Edan G, Clanet M, Dubois B, et al. Natural history of multiple sclerosis with childhood onset. *N Eng J Med* 2007; 356: 2603–2613.
- Simone IL, Carrara D, Tortorella C, Liguori M, Lepore V, Pellegrini F, et al. Course and prognosis in early-onset MS: comparison with adult-onset forms. *Neurology* 2002; 59: 1922–1928.
- Trojano M, Paolicelli D, Bellacosa A, Fuiani A, Cataldi S and Di Monte E. Atypical forms of multiple sclerosis or different phases of a same disease? *Neurol Sci* 2004; 25(Suppl. 4): S323–S325.
- Waubant E, Chabas D, Okuda DT, Glenn O, Mowry E, Henry RG, et al. Difference in disease burden and activity in pediatric patients on brain magnetic resonance imaging at time of multiple sclerosis onset vs adults. *Arch Neurol* 2009; 66: 967–971.
- Yeh EA, Weinstock-Guttman B, Ramanathan M, Ramasamy DP, Willis L, Cox JL, et al. Magnetic resonance imaging characteristics of children and adults with paediatric-onset multiple sclerosis. *Brain* 2009; 132: 3392–3400.
- Waubant E, Hietpas J, Stewart T, Dyme Z, Herbert J, Lacy J, et al. Interferon beta-1a in children with multiple sclerosis is well tolerated. *Neuropediatrics* 2001; 32: 211–213.
- Mikaeloff Y, Moreau T, Debouverie M, Pelletier J, Lebrun C, Gout O, et al. Interferon-beta treatment in patients with childhood-onset multiple sclerosis. *J Pediatr* 2001; 139: 443–446.
- Ghezzi A, Amato MP, Capobianco M, Gallo P, Marrosu G, Martinelli V, et al. Disease-modifying drugs in childhood-juvenile multiple sclerosis: results of an Italian co-operative study. *Mult Scler* (Houndmills) 2005; 11: 420–424.
- Ghezzi A, Amato MP, Capobianco M, et al. Treatment of early-onset multiple sclerosis with intramuscular interferon-beta-1a: long-term results. *Neurol Sci*. 2007 Jun;28(3):127–32.
- Ghezzi A, Amato MP, Annovazzi P, Capobianco M, Gallo P, La Mantia L, et al. Long-term results of immunomodulatory treatment in children and adolescents with multiple sclerosis: the Italian experience. *Neurol Sci* 2009; 30: 193–199.
- Pohl D, Rostasy K, Gartner J and Hanefeld F. Treatment of early onset multiple sclerosis with subcutaneous interferon beta-1a. *Neurology* 2005; 64: 888–890.
- Tenenbaum SN and Segura MJ. Interferon beta-1a treatment in childhood and juvenile-onset multiple sclerosis. *Neurology* 2006; 67: 511–513.
- Banwell B, Reder AT, Krupp L, Tenenbaum S, Eraksoy M, Alexey B, et al. Safety and tolerability of interferon beta-1b in pediatric multiple sclerosis. *Neurology* 2006; 66: 472–476.
- Kornek B, Bernert G, Balassy C, Geldner J, Prayer D and Feucht M. Glatiramer acetate treatment in patients with childhood and juvenile onset multiple sclerosis. *Neuropediatrics* 2003; 34: 120–126.

30. Waldman AT, Gorman MP, Rensel MR, Austin TE, Hertz DP and Kuntz NL. Management of pediatric central nervous system demyelinating disorders: consensus of United States neurologists. *J Child Neurol* 2011; 26: 675–682.
31. Ghezzi A, Banwell B, Boyko A, Amato MP, Anlar B, Blinkenberg M, et al. The management of multiple sclerosis in children: a European view. *Mult Scler* 2010; 16: 1258–1267.
32. Yeh EA, Waubant E, Krupp LB, Ness J, Chitnis T, Kuntz N, et al. Multiple sclerosis therapies in pediatric patients with refractory multiple sclerosis. *Arch Neurology* 2011; 68: 437–444.
33. Bykova OV, Kuzenkova LM and Maslova OI. [The use of beta-interferon-1b in children and adolescents with multiple sclerosis]. *Zh Nevrol Psikhiatr Im S S Korsakova* 2006; 106: 29–33.
34. Callen DJ, Shroff MM, Branson HM, Li DK, Lotze T, Stephens D, et al. Role of MRI in the differentiation of ADEM from MS in children. *Neurology* 2009; 72: 968–973.
35. Callen DJ, Shroff MM, Branson HM, Lotze T, Li DK, Stephens D, et al. MRI in the diagnosis of pediatric multiple sclerosis. *Neurology* 2009; 72: 961–967.
36. Wilejto M, Shroff M, Buncic JR, Kennedy J, Goia C and Banwell B. The clinical features, MRI findings, and outcome of optic neuritis in children. *Neurology* 2006; 67: 258–262.
37. Mikaeloff Y, Adamsbaum C, Husson B, Vallee L, Ponsot G, Confavreux C, et al. MRI prognostic factors for relapse after acute CNS inflammatory demyelination in childhood. *Brain* 2004; 127: 1942–1947.
38. Cohen BA, Khan O, Jeffery DR, Bashir K, Rizvi SA, Fox EJ, et al. Identifying and treating patients with suboptimal responses. *Neurology* 2004; 63(Suppl. 6): S33–S40.
39. Freedman MS, Cohen B, Dhib-Jalbut S, Jeffery D, Reder AT, Sandberg-Wollheim M, et al. Recognizing and treating suboptimally controlled multiple sclerosis: steps toward regaining command. *Curr Med Res Opin* 2009; 25: 2459–2470.
40. Rio J, Nos C, Tintore M, Borrás C, Galán I, Comabella M, et al. Assessment of different treatment failure criteria in a cohort of relapsing-remitting multiple sclerosis patients treated with interferon beta: implications for clinical trials. *Ann Neurol* 2002; 52: 400–406.
41. Ghezzi A, Pozzilli C, Grimaldi LM, Brescia Morra V, Bortolon F, Capra R, et al. Safety and efficacy of natalizumab in children with multiple sclerosis. *Neurology* 2010; 75: 912–917.
42. Yeh EA, Waubant E, Krupp LB, Ness J, Chitnis T, Kuntz N, et al. Multiple sclerosis therapies in pediatric patients With refractory multiple sclerosis. *Arch Neurol* 2011; 68: 437–444.
43. Polman CH, Bertolotto A, Deisenhammer F, Giovannoni G, Hartung HP, Hemmer B, et al. Recommendations for clinical use of data on neutralising antibodies to interferon-beta therapy in multiple sclerosis. *Lancet Neurol* 2010; 9: 740–750.
44. Borriello G, Prosperini L, Luchetti A and Pozzilli C. Natalizumab treatment in pediatric multiple sclerosis: a case report. *Eur J Paediatr Neurol* 2009; 13: 67–71.
45. Huppke P, Stark W, Zurcher C, Huppke B, Bruck W and Gartner J. Natalizumab use in pediatric multiple sclerosis. *Arch Neurol* 2008; 65: 1655–1658.
46. Makhani N, Gorman MP, Branson HM, Stazzone L, Banwell BL and Chitnis T. Cyclophosphamide therapy in pediatric multiple sclerosis. *Neurology* 2009; 72: 2076–2082.
47. Chabas D, Castillo-Trivino T, Mowry EM, Strober JB, Glenn OA and Waubant E. Vanishing MS T2-bright lesions before puberty: a distinct MRI phenotype? *Neurology* 2008; 71: 1090–1093.
48. Chabas D, Ness J, Belman A, Yeh EA, Kuntz N, Gorman MP, et al. Younger children with MS have a distinct CSF inflammatory profile at disease onset. *Neurology* 2010; 74: 399–405.
49. McLaughlin KA, Chitnis T, Newcombe J, Franz B, Kennedy J, McArdel S, et al. Age-dependent B cell autoimmunity to a myelin surface antigen in pediatric multiple sclerosis. *J Immunol* 2009; 183: 4067–4076.
50. Chitnis T and Bar-Or A. Pediatric MS: Biological presentation and research up-date. In: Chabas D and Waubant E (eds), Cambridge University Press. *Pediatric Multiple Sclerosis* 2011.
51. Banwell B, Bar-Or A, Giovannoni G, Dale RC and Tardieu M. Therapies for multiple sclerosis: considerations in the pediatric patient. *Nature Rev Neurol* 2011; 7: 109–122.
52. USFDA. *Guidance for Industry: General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products*. Washington, DC: US Department of Health and Human Services FaDACfDEaRC, Center for Biologics Evaluation and Research (CBER) 1998.
53. Koukouritaki SB, Simpson P, Yeung CK, Rettie AE and Hines RN. Human hepatic flavin-containing monooxygenases 1 (FMO1) and 3 (FMO3) developmental expression. *Pediatr Res* 2002; 51: 236–243.
54. Lambert GH, Schoeller DA, Kotake AN, Flores C and Hay D. The effect of age, gender, and sexual maturation on the caffeine breath test. *Dev Pharmacol Ther* 1986; 9: 375–388.
55. Arant BS, Jr. Developmental patterns of renal functional maturation compared in the human neonate. *J Pediatr* 1978; 92: 705–712.
56. Taub DD and Longo DL. Insights into thymic aging and regeneration. *Immunological reviews*. 2005; 205: 72–93.
57. Weksler ME. Changes in the B-cell repertoire with age. *Vaccine* 2000; 18: 1624–1628.
58. Vallejo AN. Age-dependent alterations of the T cell repertoire and functional diversity of T cells of the aged. *Immunol Res* 2006; 36: 221–228.
59. Goronzy JJ, Lee WW and Weyand CM. Aging and T-cell diversity. *Exp Gerontol* 2007; 42: 400–406.
60. Gorczynski RM, Kennedy M and MacRae S. Altered lymphocyte recognition repertoire during ageing. III. Changes in MHC restriction patterns in parental T lymphocytes and diminution in T suppressor function. *Immunology* 1984; 52: 611–620.
61. Cossarizza A, Ortolani C, Paganelli R, Barbieri D, Monti D, Sansoni P, et al. CD45 isoforms expression on CD4+ and CD8+ T cells throughout life, from newborns to centenarians: implications for T cell memory. *Mech Ageing Dev* 1996; 86: 173–195.
62. Faria AM, de Moraes SM, de Freitas LH, Speziali E, Soares TF, Figueiredo-Neves SP, et al. Variation rhythms of lymphocyte subsets during healthy aging. *Neuroimmunomodulation* 2008; 15: 365–379.
63. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Eng J Med* 2006; 354: 899–910.

64. Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue EW, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Eng J Med* 2006; 354: 911–923.
65. Gorelik L, Lerner M, Bixler S, Crossman M, Schlain B, Simon K, et al. Anti-JC virus antibodies: implications for PML risk stratification. *Ann Neurol* 2010; 68: 295–303.
66. Kean JM, Rao S, Wang M and Garcea RL. Seroepidemiology of human polyomaviruses. *PLoS Path* 2009; 5: e1000363.
67. Knowles WA, Pipkin P, Andrews N, Vyse A, Minor P, Brown DW, et al. Population-based study of antibody to the human polyomaviruses BKV and JCV and the simian polyomavirus SV40. *J Med Virol* 2003; 71: 115–123.
68. Ellis R and Boggild M. Therapy-related acute leukaemia with Mitoxantrone: what is the risk and can we minimise it? *Mult Scler* 2009; 15: 505–508.
69. Marriott JJ, Miyasaki JM, Gronseth G and O'Connor PW. 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.
70. Kornek B, Bernert G, Rostasy K, Mlczech E, Feucht M, Prayer D, et al. Long-term follow-up of pediatric patients treated with mitoxantrone for multiple sclerosis. *Neuropediatrics* 2011; 42: 7–12.
71. Hauser SL, Dawson DM, Leirich JR, Beal MF, Keyv SV, Propper RD, et al. Intensive immunosuppression in progressive multiple sclerosis. A randomized, three-arm study of high-dose intravenous cyclophosphamide, plasma exchange, and ACTH. *N Eng J Med* 1983; 308: 173–180.
72. Weiner HL, Mackin GA, Orav EJ, Hafler DA, Dawson DM, LaPierre Y, 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.
73. Baca V, Lavallo C, Garcia R, Catalan T, Saucedo JM, Sanchez G, et al. Favorable response to intravenous methylprednisolone and cyclophosphamide in children with severe neuropsychiatric lupus. *J Rheumatol* 1999; 26: 432–439.
74. Yildirim-Toruner C and Diamond B. Current and novel therapeutics in the treatment of systemic lupus erythematosus. *J Allergy Clin Immunol* 2011; 127: 303–312; quiz 13–14.
75. Adams A, MacDermott EJ and Lehman TJ. Pharmacotherapy of lupus nephritis in children: a recommended treatment approach. *Drugs* 2006; 66: 1191–1207.
76. Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Eng J Med* 2008; 358: 676–688.
77. Tzaribachev N, Koetter I, Kuemmerle-Deschner JB and Schedel J. Rituximab for the treatment of refractory pediatric autoimmune diseases: a case series. *Cases J* 2009; 2: 6609.
78. Carson KR, Focosi D, Major EO, Petrini M, Richey EA, West DP, et al. Monoclonal antibody-associated progressive multifocal leucoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a Review from the Research on Adverse Drug Events and Reports (RADAR) Project. *Lancet Oncol* 2009; 10: 816–824.
79. Rosen H, Alfonso C, Surh CD and McHeyzer-Williams MG. Rapid induction of medullary thymocyte phenotypic maturation and egress inhibition by nanomolar sphingosine 1-phosphate receptor agonist. *Proc Natl Acad Sci USA* 2003; 100: 10,907–10,912.

## Co-Investigator Appendix

1. Michael Absoud, FRCPC (University of Birmingham, UK)
2. Maria Pia Amato, MD (University of Florence, Italy)
3. Barbara Bajer-Kornek, MD (Medical University of Vienna, Austria)
4. Amit Bar-Or, MD, FRCPC (Montreal Neurological Institute and Hospital, McGill University, Canada)
5. Leslie Benson MD (Children's Hospital Boston, USA)
6. Astrid Blaschek MD (Dr von Haunersches Children's Hospital, Ludwig-Maximilians University, Germany)
7. Russell C Dale, MRCP, PhD (Children's Hospital at Westmead, Australia)
8. Kumaran Deiva, MD, PhD (AP-HP, Hôpital Bicêtre, National Referral Center for Neuro-Inflammatory diseases in children (NIE), Department of Pediatric Neurology, France)
9. Massimo Filippi, MD (Neuroimaging Research Unit, Division of Neuroscience, INSPE, Scientific Institute and University, Hospital San Raffaele, Italy)
10. Natan Gadoth, MD (Maynei Hayesuah Medical Center, Israel)
11. Ananthanarayanan Girija, MD (Senior Consultant Neurologist, Malabar Institute of Medical Sciences, India)
12. Ariel Gomez Garcia, MD (J.M. Pérez Paediatric Hospital, Cuba)
13. Veronica Gonzalez, MD (Hospital Sant Joan de Dèu, Spain)
14. Andrew Goodman, MD (University of Rochester, USA)
15. Mark P. Gorman, MD (Children's Hospital Boston, USA)
16. Rogier Hintzen, MD, PhD (Department of Neurology, Erasmus University Medical Centre, Rotterdam, The Netherlands)
17. Mohammed Jan, MB, ChB, FRCPC (Department of Pediatrics, Faculty of Medicine, King Abdulaziz University, Saudi Arabia)
18. Anneli Kolk, MD, PhD (Tartu University Hospital, Estonia)
19. Ming Lim, BMBS, PhD (Evelina Children's Hospital at Guys and St Thomas' NHS Foundation Trust, Kings Health Partners, London, UK)
20. Jean Mah, MD, MSc, FRCPC (University of Calgary, Alberta Children's Hospital, Canada)
21. Naila Makhani, MD, FRCPC, MPH (Hospital for Sick Children, Canada)
22. Maria Giovanna Marrosu, MD (University of Cagliari, Italy)
23. Nicoletta Milani, MD (Child Neurology Dept, Fondazione IRCCS Istituto Neurologico, Italy)
24. Manikum Moodley, MBCHB, FCP(SA), FRCP(UK) (Pediatric MS Program, Pediatric Neurology Center, Neurological Institute, Cleveland Clinic, USA)

25. Rinze Neuteboom, MD (Pediatric MS Centre Rotterdam, Erasmus University Medical Centre, The Netherlands)
26. Katerina Paderova, MD (University Hospital Motol, Czech Republic)
27. Marc Patterson, MD, FRACP (Mayo Clinic, USA)
28. Francesco Patti MD (Policlinico-Vittorio Emanuele, Centro Sclerosi Multipla, Università di Catania, Italy)
29. Joaquin Pena, MD (Demyelinating Disorders Clinic, Hospital de Especialidades Pediátricas, Venezuela)
30. Anne-Louise Ponsonby, BMed Sci, MBBS, PhD, FAFPHM (Murdoch Childrens Research Institute, Royal Children's Hospital, Australia)
31. Maura Pugliatti, MD, PhD (Dept of Neuroscience, University of Sassari, Italy; Dept of Public Health and Primary Health Care, University of Bergen, Norway)
32. Maria A. Rocca, MD. (Neuroimaging Research Unit, Division of Neuroscience, INSPE, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Italy)
33. Moses Rodriguez, MD (Mayo Clinic, USA)
34. Isabella Laura Simone, MD (Department of Neurosciences, Bari, Italy)
35. Gabriella Spinicci, MD (Multiple Sclerosis Centre, Hospital Binaghi, Italy)
36. Sunita Venkateswaran, MD (Children's Hospital of Eastern Ontario, Canada)
37. Amy Waldman, MD, MSCE (Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, USA)
38. Bianca Weinstock-Guttman, MD (Baird MS Center, University of Buffalo, USA)