Disease-Modifying Therapy of Pediatric Multiple Sclerosis

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Abstract Multiple sclerosis (MS) is increasingly recognized in children and adolescents. Improved awareness, access to care, and subspecialty training in pediatric MS has allowed for better access to treatment. Children with MS present with an overwhelmingly relapsing form of the disease and have more frequent relapses than their adult counterparts during the early phases of disease. Cognitive deficits are prominent in pediatric MS, as opposed to locomotor disability. Beta interferons and glatiramer acetate are frequently used off-label drugs. Additional second-line therapies have occasionally been used in treatment failures. No randomized clinical trials have been performed to date in pediatric MS; however, recent legislation necessitates pediatric studies for new agents, which will allow for better defined pharmacokinetic, dosing, and efficacy data to guide the treating neurologist.

Keywords Pediatric · disease-modifying therapy · multiple sclerosis · children · adolescent.

Introduction

It is increasingly recognized that multiple sclerosis (MS) can present in childhood or adolescence. The youngest onset of MS in the medical literature is 2 years of age, however, the majority of children are diagnosed in their early teens [1].

Studies have estimated the prevalence of pediatric onset MS ranging from 2.7 to 10.5 % [2–7] of the total MS populations. In the United States, based on a study using a large California-based database, it is reported that an incidence of pediatric MS is 0.51/100,000 of the population [8]. In Canada, 1.8/10⁶ children are estimated to have MS [9]. A study from Germany estimated the incidence of pediatric MS as 0.3/100,000 [10]. Although MS onset across the ages remains a continuum, there are important developmental, biological, social, and governmental regulatory issues pertaining to the pediatric population, which necessitate focused studies in this age group.

Clinical Presentation and Course

The initial clinical course of the vast majority of children with MS is relapsing-remitting MS in 85.7 to 100 % of cases [2, 3, 11], which are somewhat higher rates than those reported in adults. Presenting symptoms include optic neuritis, sensory disturbances, and motor and cerebellar symptoms [6, 12–16]. Children can frequently present with polyfocal symptoms, and a small proportion of children with encephalopathy may go on to develop MS [17, 18].

In retrospective studies, the annualized relapse rate in pediatric-onset MS estimates are between 0.38 and 0.87 for the whole relapsing-remitting period in these few studies with mean disease duration of 10 years or more [3, 5, 19]. A prospective study of patients with MS seen at a large MS center showed that patients with an onset before 18 years had a twofold to threefold higher relapse rate during the first 3 years of their disease than adults seen at the same institution with pediatric annualized relapse rate (ARR) of 1.1 and adult ARR of 0.4 [16]. Recovery from relapses also appears to be more rapid in children than in adult MS patients (mean time of relapse-related symptoms, 4.3 weeks in pediatric MS vs 6 to

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8 weeks in adult MS patients) [20]. Several features, including optic neuritis, cerebral localization, presence of encephalopathy, and nonwhite race, were associated with a more severe first attack, and a poor recovery from the first attack predicted poor recoveries from subsequent attacks [21].

Although the rate of disability progression varies from individual to individual, regardless of the age at onset, a consistent finding in most pediatric MS retrospective studies is lower disability scores compared with adult MS patients while controlling for disease duration. The median time to reach an Expanded Disability Status Scale (EDSS) of 4 was approximately 20 years for pediatric MS *versus* 10 years for adult MS patients [7]. Similar data was obtained from the European database for Multiple Sclerosis (EDMUS) consisting of 394 patients with a pediatric MS onset (defined as less than 16 years of age) compared with a cohort of 1775 adult MS [11]. The median times from onset to disability scores of 4, 6, and 7 were 20, 29.9, and 37 years, respectively. The time to reach Disability Status Scale (DSS) of 4 was 10 years longer compared to the adult MS population, and it was even longer for children younger than 12 (28 years). However, the pediatric MS patients reached these disability scores at approximately 10 years younger (i.e., ages 34.6, 42.2, and 50.5 to reach the DSS of 4, 6, and 7, respectively). However, despite the slower development of irreversible disability in pediatric MS patients, the age when these patients are confronted with disease progression and neurological deficits is 10 years younger than those with adult-onset MS. This often occurs at the time when these young adults may be considering to have a family and enter the workforce. The impact of using disease-modifying therapies for MS to delay the disease progression in pediatric-onset MS has yet to be studied.

Cognitive dysfunction can present early in the course of pediatric multiple sclerosis [22–25]. One study of 37 children with MS found that 60 % of these children experience cognitive difficulties in 1 major domain, and 35 % have difficulties in 2 domains [23]. The areas that were most commonly affected were complex attention, naming, delayed recall, and visual memory. In contrast, verbal fluency and immediate recall were relatively intact. Another study of 61 children with MS compared to age-matched healthy controls found that 31 % of patients exhibited significant impairment in three assessed domains of cognitive functioning, and 53 % failed at least 2 tests [25]. Longitudinal data along a 2-year period of time has shown that more than 60 % of children continue to accrue cognitive deficits [26].

Given the high incidence of cognitive deficits reported in studies, neuropsychological testing should be considered for all children with MS and related demyelinating diseases. Moreover, children with identified issues may benefit from the implementation of an individualized educational plan and in some cases cognitive rehabilitation may be warranted [27].

MRI Features

Comparative magnetic resonance imaging (MRI) studies have shown a higher T2 lesion burden in children with MS compared with adults [28, 29], supporting the concept that MS in children is more inflammatory than that in adults. MRI lesions in children with MS are generally located in the periventricular and subcortical white matter. However, few studies have formally compared the extent and distribution of lesions in children who have MS compared with adults who have MS. Brain lesions in younger children (age, <11 years) are large with poorly-defined borders, and the lesions are frequently confluent at the onset of disease [14]. Such T2-bright foci in younger children may vanish on repeat scans, unlike that seen in teenagers or adults. This suggests that disease processes in the developing brain, including immune response, may be different from those in older patients. Three Tesla MRI studies suggest that pediatric patients have a lower number of cortical lesions than adults [30]. However, diffusion tensor imaging (DTI) studies in children with MS demonstrated damage in the normal appearing white matter (NAWM) of the interhemispheric, projection and intrahemispheric white matter tracts [31, 32]. Brain atrophy appears to be slower in children who have MS compared with adults who have MS, despite equal or higher T2 lesion load [29]. There are no longitudinal studies assessing lesion or atrophy accrual in children with MS.

Only 67 % of children met the adult 2005 MS McDonald MRI criteria at the time of their MS defining attack, suggesting a low lesion burden than adults at the time of diagnosis [33]. A study recently evaluated the 2010 McDonald MRI criteria in the pediatric population, and found that in children >11 years of age and in those with non-acute disseminated encephalomyelitis (ADEM) presentations, there was high sensitivity and specificity for the dissemination in space and time criteria for the development of MS [34].

First-Line Disease-Modifying Treatment

Currently, there are no approved treatments by the Food and Drug Administration for MS in children and only limited approval for beta interferon use in adolescents by the European Medicines Agency (EMA). First line-treatments, including beta interferons (Avonex (Biogen Idec, Cambridge, MA, USA); Betaseron/Bayer, West Haven, CT, USA; and Rebif (Serono, Rockland, MA, USA)) and glatiramer acetate (Copaxone (Teva, North Wales, PA, USA)), are commonly used in the pediatric population, which is demonstrated by national and international surveys [35, 36]. However, in some parts of the world, use of disease-modifying treatments are more restricted in children. To date, there have been no randomized control trials of any disease-modifying treatments in the pediatric population and

use of the treatments is mainly based on small retrospective, observational studies.

Beta Interferons

Beta interferons are widely used as the first-line therapy in adult MS. The clinical benefit of interferon beta therapy in relapsing-remitting MS may be mediated via several mechanisms, including the inhibition of proinflammatory cytokines, induction of anti-inflammatory mediators, reduction of lymphocyte migration, and inhibition of auto-reactive T-cells [37]. In adult MS, studies have demonstrated an approximate 30 % reduction in exacerbation rate compared to the placebo for periods of 2 to 3 years [38–40].

Retrospective case series in children with sample sizes ranging from 9 to 77 suggest that interferon beta-1a and beta-1b are safe and well-tolerated in the pediatric population at the same doses that are used in adults. [41–47] Reported side effects include flu-like symptoms (35–65 %), leucopenia (8–27 %), thrombocytopenia (16 %), anemia (12 %), and transient elevation in transaminases (21–33 %) [41, 42, 44, 48]. Injection site reactions (>2/3), abscesses (6 %), and injection site necrosis (6 %) may occur more often in children taking the subcutaneous formulation [44]. Depressive mood disorder was only assessed in studies of subcutaneous interferon beta-1a and it was found in 2 to 4 % [44, 48] of pediatric patients. One retrospective study of subcutaneous interferon beta-1b stratified side effects in children <10 years old and >10 years old [42]. Younger children had a 63 % incidence of liver function test elevation, compared with 10 % in the older age group. Flu-like symptoms and injection-site reactions were similar in both groups.

Open-label studies have demonstrated a reduction in relapse rate among patients treated with intramuscular beta-interferon-1a [45–47, 49, 50] and subcutaneous interferon beta-1a, in the range of 2.5 to 1.9 pre-treatment ARR to 0.4 to 0.04 post-treatment ARR.

There have been no studies of titration schedules in pediatric MS. In published studies, the majority of patients were escalated to full dose. There are only 2 published studies of varied doses of beta interferons in children with MS [44, 48]. Little information regarding neutralizing antibodies to interferon in this population is available, although 1 study has suggested that positive neutralizing antibodies are far less commonly seen in the pediatric MS population than in the adult MS population [51].

Glatiramer Acetate

Glatiramer acetate (Copaxone, Teva) is the acetate salt of a mixture of synthetic polypeptides composed of L-alanine, L-glutamic acid, L-lysine, and L-tyrosine. Glatiramer acetate is designed to mimic human myelin basic protein and is postulated to induce myelin-specific response of suppressor T-

lymphocytes, inhibit specific effector T-lymphocytes, and act via an effect on antigen-presenting cells [52]. In adult relapsing-remitting MS patients, a 29 % reduction of the number of relapses in the treated group *versus* the placebo has been found for a 2-year period of [53]. One small retrospective study describing the use of glatiramer acetate in 7 children with MS found transient systemic reaction in 1 patient and injection site reactions in 4 patients [54]. Two studies from Italy described 9 patients [46] and 14 patients [45] treated with glatiramer acetate. In each study, 1 patient experienced transient systemic reactions after Copaxone (Teva) injections. No other major side effects were reported. Full daily dosing of Copaxone (Teva) was administered in each study.

Inadequate Treatment Response in Pediatric MS

Although placebo-controlled, double-blind studies have not been performed in children, the majority of studies have demonstrated a reduction in relapse rate after the initiation of first-line treatments. However, some children continue to experience breakthrough disease. The definition of treatment failure is not uniform across clinicians and centers, however, evidence of ongoing relapses, MRI activity, and disability accrual may suggest switching first-line treatment or escalating to second-line therapy. There is a lack of consensus on the definition of an inadequate treatment response for adult MS. Published consensus statements and studies in adult MS have suggested that 1 to 2 annual relapses or no improvement in relapse frequency can be considered treatment failures [55–57]. In addition the occurrence of 2 or more T2 brain MRI lesions or 1 or more Gd+ lesions during the first year of treatment can also be considered treatment failures [58]. In a retrospective study of 258 pediatric MS patients, 44 % switched to another first- or second-line therapy during a 3-year period because of an inadequate treatment response or lack of adherence as determined by treating physicians [59]. 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. Moreover, these underscore the need to identify measures to improve adherence to MS treatments in the pediatric population.

Emerging MS Therapies

There are several new treatments 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.

Natalizumab

Natalizumab (Tysabri, Biogen-Idec, Cambridge, MA, USA) is a monoclonal antibody that targets $\alpha 4\beta 1$ -integrin. It is approved for the treatment of relapsing forms of MS [60], and effectively blocks T- and B-cell migration across the blood-brain barrier. There are several reports of natalizumab treatment in adolescents with MS [61, 62]. The largest study included 19 pediatric subjects with MS (mean age, 14.6 years) treated with monthly natalizumab at a dose of 300 mg [63]. Baseline ARR was 5.2 ± 1.9 . All the patients remained relapse-free during the whole follow-up. The median EDSS decreased from 2.5 to 2.0 at the last visit ($p < 0.001$). EDSS remained stable or decreased for all patients during the follow-up, and no new gadolinium-enhancing lesions were detected. No major side effects were reported. Another study assessed use in 3 patients with very active disease, the youngest of whom was 12 years old at the start of natalizumab [61]. Natalizumab was administered on a weight basis at a dose of 3 to 5 mg/kg, and all relapses ceased during the following 15 to 24 months of follow-up. An open-label study of natalizumab in adolescents with Crohn's disease dosed the drug at 3 mg/kg with a safety and efficacy profile similar to adult studies [64].

Side effects of natalizumab include hypersensitivity reactions and development of antibody to the drug. 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 has been developed and may stratify patients into low- and high-risk groups for PML [65]. The JC virus antibody test has been applied to adults, and has demonstrated differential risks of developing PML in the JC virus antibody-positive patients according to duration of natalizumab use and prior exposure to an immunosuppressive agent [66, 67].

Two large, population-based studies have demonstrated that children and adolescents have lower rates of JC virus infection than adults [68, 69], however, specific JC virus infection rates are unknown in children and adolescents with MS. An enhanced understanding of the risk of PML during primary JC virus acquisition is required because 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.

Fingolimod

Fingolimod (Gilenya, Novartis, East Hanover, NJ, USA) is an orally administered small molecule that targets the sphingosine-1-phosphate receptor that is necessary for lymphocyte egress from lymph nodes [70–72]. This drug may specifically target Th17 central memory cells [73]. Gilenya (Novartis, East Hanover, NJ, USA) was approved for adult patients with MS in the United States, Europe, and Russia in 2010, and in

Australia and Canada in 2011. No information regarding safety, tolerability, and optimal dosing in children currently exists.

Teriflunomide

Teriflunomide (Aubagio Genzyme, a Sanofi company, Cambridge, MA, USA) is an oral de novo inhibitor of the dihydroorotate dehydrogenase enzyme involved in pyrimidine synthesis. Teriflunomide exerts anti-inflammatory, possibly through reduction of activated lymphocytes in the central nervous system. This agent was approved in the United States in 2012 for use in adult MS patients. No information regarding safety, tolerability, and optimal dosing in children currently exists.

Cyclophosphamide

Cyclophosphamide (Cytoxan, Bristol Myers Squibb, Princeton, NJ, USA) is not approved for the treatment of MS. However, pulse cyclophosphamide has been shown to reduce disease activity in adult MS in class I studies [74, 75]. Adults 40 years of age or younger were better responders than those older than 40 years of age [75]. We conducted a retrospective study of 17 children, aged 9 to 18 years, treated with cyclophosphamide at either pulse or induction therapy [76]. In the majority of cases, the relapse frequency and EDSS improved 1 year after the initiation of cyclophosphamide therapy. However, side effects included vomiting, transient alopecia, osteoporosis, and amenorrhea. One patient developed bladder carcinoma that was successfully treated. There has been considerable experience with cyclophosphamide in other pediatric autoimmune diseases [77–79], 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, Genentech, South San Francisco, CA, USA) is an antibody that primarily targets the CD20 receptor on activated B cells, effectively depleting this subset for a period of 6 to 12 months. Rituximab 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 [80]. Reduction in relapse rate has been reported in an adolescent treated with rituximab, without significant side effects [81]. Nevertheless, cases of PML have been reported in patients with systemic lupus erythematosus (SLE) and other autoimmune diseases treated with rituximab [82]. The possible relationship of rituximab treatment and the development of PML and other severe infections raise particular concern regarding its use in children.

Studies are required to evaluate optimal dosing, safety, and efficacy of rituximab in pediatric MS.

Daclizumab

Daclizumab is a monoclonal antibody that blocks the interleukin (IL)-2 receptor alpha chain (CD25) present in the high-affinity IL-2 receptor on T cells, thus inhibiting T-cell replication and making more IL-2 available to the low-affinity CD25 receptor present on NK cells, which induces a regulatory NK cell population [83]. One form of this antibody, intravenous daclizumab has been used off-label in adult MS patients [84–86], and another subcutaneous form is being tested in clinical trials in adult MS [87, 88]. Adverse effects have been reportedly associated with intravenous daclizumab therapy, including elevated liver function tests, infections, psoriasis, and oral ulcers [84–86].

Recently, we presented the results of 7 pediatric MS patients treated with intravenous daclizumab, largely in combination with beta interferons. Treatment with daclizumab was associated with reductions in ARR, number of contrast enhancing lesions, and reduction or stabilization of EDSS in each patient. However, 4 patients had relapses and new contrast enhancing lesions during daclizumab treatment [89]. Intravenous daclizumab has been used safely and successfully in pediatric patients with solid-organ transplants [90] and autoimmune uveitis [91]. A review of pending clinical trial results in adults is required to assess the potential role of subcutaneous daclizumab in the pediatric MS population.

Symptomatic Management

Pediatric MS is a lifelong chronic disease, and along with relapses and disease progression, patients may experience a variety of chronic symptoms, including fatigue, depression, bladder urgency or retention, bowel constipation or dys-synergy, and neuropathic pain. Many of these symptoms may be ameliorated with symptomatic treatments. In addition, evaluation by subspecialties, including urology, pain clinic, neuro-ophthalmology, and rehabilitation may play an important role in the management of the pediatric patient.

Evaluating New Treatments in Pediatric MS

Recent legislation in the United States and Europe has now mandated pediatric studies in new biological agents. In Europe, a pediatric investigation plan must be submitted to the EMA. Similarly, the Pediatric Research Equity Act in the United States requires pediatric studies for any new

active molecule, new dosage form, or new route of administration. A full or partial waiver is possible if the treated condition does not occur in the pediatric population or if studies are not feasible or appropriate or safe for the age group. In addition, the Best Pharmaceuticals Act for Children in the United States allows for the submission of Proposed Pediatric Study Request with the incentive of eligibility for an additional 6 months of market exclusivity.

There is lack of clarity on how to conduct clinical trials in the pediatric MS population, given the small numbers of patients, ethical and practical challenges of pediatric studies, and lack of well-defined natural history studies. A recent consensus statement published by the International Pediatric MS Study Group surveyed opinions among 50 neurologists treating MS in children, and recommended basic guidelines for the conduct of studies [35]. Neurologists agreed that high impact pharmacokinetic and efficacy studies were required to evaluate promising new agents. In general, adequate safety and efficacy data was required from adult clinical trials prior to the consideration of initiation of studies in children. Treatments with prior use in other pediatric populations may be the exception.

The International Pediatric MS Study Group held a meeting in January 2012, which included members from the Food and Drug Administration, the European Medicines Agency, and the pharmaceutical industry, as well as academic leaders in the field to further define the specifics of clinical trial design. Based on published literature and informative discussion with the attendees, the academic leaders established guidelines for outcome measures, including clinical, cognitive, and MRI to be considered in the pediatric MS clinical trials (Chitnis et al., under review). The pros and cons and ethical issues in clinical trial designs were discussed and presented. The development of an international unified long-term drug registry was deemed a necessity.

Conclusions

Children and adolescents with MS experience a more inflammatory course of the disease than their adult counterparts. They appear to accrue locomotor disability more slowly, but they can have significant cognitive deficits, even early on in the course of the disease. There have been no randomized-controlled studies of disease-modifying therapies. However, first-line therapies, beta interferon, and glatiramer acetate are extensively used off-label. Guidelines surrounding the development of robust clinical studies for safe and effective therapies in pediatric MS are being developed and may be implemented in the next few years, which may allow even the youngest of patients to benefit from the advances in MS care.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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