Therapeutic Advances in Pediatric Multiple Sclerosis

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Multiple sclerosis (MS) is a disease characterized by recurrent immune-mediated episodes of central nervous system demyelination. Over the past decade, we have made substantial progress in our ability to identify and treat MS in pediatric patients. MS historically has been considered a disease of adulthood, but we now know that it affects children at an annual rate of 1-2/100 000.[1,2]

Although MS carries the potential for high morbidity, a growing number of increasingly potent and sophisticated therapies are available for these patients. In this review we focus on recent therapeutic advances in pediatric MS, including approved, off-label, and emerging therapies. We also discuss necessary steps for advancing the current state of clinical and therapeutic knowledge.

Overview of Clinical Features, Diagnosis, and Risk Factors in Pediatric MS

The clinical features and natural history of pediatric MS have been described in several cohorts and case series.[2-6] Compared with adults, pediatric patients tend to have more frequent relapses,[7] more lesions detected on T2-weighted magnetic resonance imaging (MRI),[8] and higher cerebrospinal fluid white blood cell counts at disease onset.[9] Pediatric patients also have a relatively high rate of cognitive impairment, with 30% showing some deficits within the first few years of disease onset.[10] Despite these aggressive features, compared with adults, pediatric patients tend to recover more quickly and completely from relapses in terms of motor, cerebellar, and sensory deficits and to have a slower rate of disability progression.[11,12] It should be noted that these data were drawn primarily from white non-Hispanic cohorts and might not be generalizable to all populations. This is particularly relevant given the evidence that some ethnic populations may be at greater risk for MS, which merits further study.[1] Unfortunately, even though progression of disability is slower in children than in adults, pediatric patients with MS still acquire major disabilities (eg, loss of independent ambulation) at a younger age than individuals with adult-onset MS.[11,12]

Diagnostic criteria for pediatric MS have been proposed previously.[13,14] In 2010, the widely used McDonald criteria for the diagnosis of MS were revised, for the first time specifically addressing the pediatric population.[15] In their simplest form, the criteria require evidence of 2 distinct immune-mediated demyelinating episodes, occurring at separate times and in separate neuroanatomic locations (ie, dissemination in both time and space). The 2010 criteria acknowledge several features unique to pediatric MS, including the occurrence of large, poorly defined MRI lesions (particularly in patients aged <11 years), a relatively high MRI lesion load at time of diagnosis, and a more rapid rate of lesion resolution compared with adults. Of note, Sadaka et al[16] recently validated the 2010 McDonald criteria in older children (aged >11 years) with pediatric MS, but found that the criteria performed poorly in younger children (aged <11 years) and in children with acute disseminated encephalomyelitis. These authors, as well as the authors of 2010 McDonald criteria, suggest using serial clinical observations to establish the diagnosis of MS in these 2 subgroups.

In both pediatric and adult MS, disease susceptibility is influenced by a variety of genetic and environmental factors.[17] Numerous previous studies support the notion that susceptibility to MS is modulated by multiple genes (at least 50). The most prominent genetic predictors of MS susceptibility involve the major histocompatibility complex II, where specific variations of the HLA-DRB1 gene allele convey the most significant risk.[18,19] Among the proposed infectious agents associated with MS susceptibility, there is no single "MS pathogen," although Epstein-Barr virus has demonstrated a consistent association with MS (as well as with other autoimmune disorders). Epstein-Barr virus antibody titers are present at consistently higher rates in individuals with MS than in the general population.[20] This association may be even more pronounced in pediatric MS,[21-23] although this may be related to the higher prevalence of HLA-DRB1 in the MS groups, given that this polymorphism is associated with higher titers in both pediatric controls and MS cases.[24] Other possible risk factors include exposure to cigarette smoke, which may increase MS risk, and exposure to cytomegalovirus, which may decrease MS risk.[25,26]

FDA	Food and Drug Administration
IFN	Interferon
JC	John Cunningham
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
PML	Progressive multifocal leukoencephalopathy
Th	T helper

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Vitamin D and Pediatric MS

Currently, the most promising modifiable MS risk factor is vitamin D exposure. Knowledge of the association between vitamin D and the risk of developing MS began with the observation that more extreme geographical latitudes (ie, regions with lower levels of vitamin D–producing sun exposure) were associated with higher rates of autoimmune disorders, including MS.[27-29] Since then, abundant evidence has accumulated linking low levels of vitamin D with MS.[30] Higher rates of MS have been linked with low vitamin D exposure in utero,[31] during infancy,[31] and in adult life.[32,33]

Most recently, vitamin D has been linked to prognosis of MS, with serum levels inversely correlated with risk of relapse,[34,35] disease severity,[36] and the development of new lesions detectable on MRI.[37] In a 2010 study, Mowry et al[38] prospectively examined 25(OH) vitamin D levels as a predictor of relapse risk a cohort of 111 pediatric patients with MS. They found that a 10-ng/mL increase in serum vitamin D level was associated with a 34% reduction in relapse risk, which is on par with the effect of the current first-line therapies for MS.

Although low vitamin D levels have been repeatedly linked with MS outcomes, a definitive causal association has yet to be established. Vitamin D is known to be a potent immunomodulator. It down-regulates antigen presentation, promotes a shift from a proinflammatory T-cell profile (T helper [Th] 1 and Th17) to an anti-inflammatory profile (Th2), up-regulates T and B regulatory cells, and induces apoptosis of mature B cells.[38] In the most widely studied animal model for MS, murine experimental autoimmune encephalomyelitis, vitamin D supplementation effectively attenuates disease.[39] Validation of vitamin D as a therapeutic agent in pediatric and adult MS is the subject of several ongoing clinical trials. If it proves effective in prospective trials, vitamin D may eventually fill an important niche as a safe, inexpensive, and well-tolerated oral therapeutic agent in our pediatric MS arsenal.

First-Line Therapies in Pediatric MS

Selection of first-line disease-modifying therapy in pediatric MS follows the pattern of practice in adult MS,[40] which entails a choice of interferon (IFN)-β1a, IFN-β1b, or glatiramer acetate, all of which are injectable therapies. Both IFN-β1a/b and glatiramer acetate work primarily by modulating T cell function, with IFN achieving this effect predominantly through direct cytokine modulation[41] and glatiramer acetate achieving it, at least in part, by favorably altering antigen presention.[42] In adult MS trials, these agents have demonstrated similar efficacy, preventing 30%-40% of new MS relapses and producing a modest attenuation of long-term disability.[43]

These drugs are US Food and Drug Administration (FDA)-approved only in adults, but have been the subject of numerous small retrospective studies in pediatric MS, as summarized in the Table.[44-51] The net result of these studies suggests an efficacy similar to that observed in adults, and supports the use of these agents in pediatric MS. Unfortunately, none of the currently available disease-modifying therapies has been subjected to large-scale randomized controlled trials in pediatric patients with MS. In practice, the IFNs are initiated with an upward titration over 4-6 weeks, and glatiramer acetate is initiated at full dosage. Most children are given a full adult dose of IFN or glatiramer acetate, unadjusted for age or body weight. The most frequent adverse effects of IFN include transient flu-like symptoms, injection site reactions, and transaminitis; serial laboratory monitoring for transaminitis over the first 6 months of treatment is common practice.[41] The adverse effects of glatiramer acetate are usually limited to systemic flushing reaction.[42] After 15 years of widespread use in the adult population, these medications have a well-established long-term safety profile.[41] Their long-term effectiveness at preventing progression of disability in pediatric MS is unclear, however.

Second-Line Therapies in Pediatric MS

Approximately one-half of children with MS require a switch to a second disease-modifying agent owing to treatment failure (28%) or poor tolerance of the therapy itself (19%).[52] These patterns of use are similar to those seen in adults.[53] Many children are subsequently switched to an alternative first-line therapy, but for those with more aggressive or refractory disease, providers are increasingly relying on newer and/or more potent therapies.

The number of immunomodulatory agents used to treat refractory pediatric MS has increased substantially over the past 10 years. These therapies include monoclonal antibody therapies (eg, natalizumab, daclizumab), chemotherapeutic agents (eg, cyclophosphamide, mitoxantrone), and oral medications with novel mechanisms of action (eg, fingolimod, teriflunomide, dimethyl fumarate). Of these, only natalizumab, mitoxantrone, fingolimod, and teriflunomide have been approved by the FDA for use in adults with MS. The safety and efficacy of these new and emerging therapies in pediatric MS are of intense interest. The existing safety and efficacy data have been reported in several prospective and retrospective studies of pediatric patients with MS. These studies are reviewed below and summarized in the Table.

Natalizumab, a monoclonal antibody targeting α-4 integrin, an adhesion molecule critical to immune cell migration into the brain, received FDA approval in 2004 for use in adults with MS. Its use has been described in several pediatric MS cohorts[54-57] and a small open-label trial,[52] where it has been well tolerated and effective in reducing relapse rate and MS disability scores in patients with refractory disease. These off-label pediatric studies were short-term and did not provide substantial long-term safety data in children, however. The most serious adverse event associated with the use of natalizumab is the increased incidence of progressive multifocal leukoencephalopathy (PML), an often-fatal opportunistic brain infection caused by the John Cunningham (JC) virus. This association prompted a brief, voluntary