THERAPEUTIC CONSIDERATIONS IN PEDIATRIC MS

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No MS clinical trials have included pediatric patients. As a result the label of all MS treatments excludes patients under the age of 18 years and drugs are used off-label for patients with pediatric MS. Numerous studies, mostly retrospective, have reported on safety and sometimes efficacy of some of these drugs approved for adult MS, albeit in limited numbers, hence not providing evidence beyond Class III & IV. A recent consensus statement from the steering committee of the international pediatric MS study group (IPMSSG) reviewed the major studies on treatment of pediatric MS.[1] Since the time of that publication, the FDA has approved new medications for adult patients with relapsing-remitting MS. Although more safety data becomes available after new drugs are approved on the market, concerns remain for some agents regarding their use in patients undergoing brain maturation. Fortunately, the American (FDA) and European (EMA) regulatory agencies now request that companies developing medications for adults also have an investigational plan for pediatric patients.[1]
Major challenges in treatment of pediatric MS include the identification of the most effective agents in young patients to prevent relapses and neuro-axonal injury while minimizing negative impact on the CNS maturational status. An individualized approach taking in account individual risk profile, and existing efficacy and safety data are critical to optimize care. Algorithms for risk stratification according to relevant factors such as age, gender, MRI and immunological markers may be developed in the future to optimize patient care.
Several features unique to pediatric MS such as the higher relapse rate and often higher disease burden on imaging suggest a more active disease. Although accrual of physical disability is usually slower than in adults, disability occurs earlier in life. These characteristics have to be considered when discussing treatment options with patients and families.

Treatment of acute relapses:
Glucocorticosteroids are widely used in the acute symptomatic treatment of relapses in pediatric MS to help shorten duration of relapse. Recommended dosing is 20-30 mg/kg/day (up to 1000 mg) of intravenous methylprednisolone for 3-5 days. Oral dexamethasone can also be used at an equivalent dose (ie up to 140 mg daily) instead of methylprednisolone. Plasma exchange is considered for pediatric patients with severe disability resulting from a recent relapse that is not recovering well after treatment with pulse steroids. The use of plasma exchange for relapse therapy is based on a randomized trial in adults with severe relapses of MS and NMO. Plasma exchange is usually administered as 5 to 7 exchanges over a period of up to 2 weeks. In younger children, venous access for plasma exchange can be challenging and cardiovascular stability deserves extra consideration in young patients. Possible side effects from plasma exchange in older children seem comparable to adults, but no large series are available. As such, plasma exchange should be reserved for residual relapse symptoms compromising daily function in experienced centers. Intravenous immunoglobulin therapy is also occasionally used in the same context but very little data suggest a real benefit from such treatment as only small case series or case reports have been published and randomized trials have not been performed, thus it is unclear whether IVIG improves the natural recovery of a relapse.

First-line Therapies to prevent relapses in Pediatric MS
Selection of first-line disease-modifying therapy in pediatric MS follows the pattern of practice in adult MS[2], which entails a choice of interferon beta-1a, interferon beta-1b, or glatiramer acetate, all of which are injectable therapies. These agents have been on the market for the longest and as such more safety data are available in children. In adult MS trials, these agents have demonstrated similar efficacy, preventing 30-40% of new MS relapses and a modest attenuation of long-term disability. These drugs are US FDA-approved only in adults, but have been the subject of numerous small, retrospective studies in pediatric MS.[3-10] The net result of these studies suggest an efficacy similar to that observed in adults and support the use of these agents in pediatric MS. Unfortunately, none of the currently available disease-modifying therapies have been subjected to large scale randomized controlled trials in pediatric MS patients. In practice, the interferons are initiated with an upward titration over 4-6 week, while glatiramer acetate is initiated at full dose. Most children are administered a full adult dose of interferon or glatiramer acetate, unadjusted for age or body weight. The most frequent adverse effects of interferon beta include transient flu-like symptoms, injection site reactions, and transaminitis; serial lab monitoring for transaminitis over the first six months of treatment is common practice. The adverse effects of glatiramer acetate are usually limited to systemic flushing reaction. After over 15 years of widespread use in the adult

population, these medications have a well-established long-term safety profile. Their long-term effectiveness at preventing progression of disability in pediatric MS is unclear.

Second-line Therapies to prevent relapses in Pediatric MS

Approximately half of children with MS require a switch to a second disease-modifying agent due to breakthrough disease (28%) or poor tolerance of the therapy itself (19%).[11] These patterns of use are similar to those seen in adults. Many children are subsequently switched to an alternate 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 in the treatment of refractory cases of pediatric MS has increased substantially over the past ten years. These therapies include monoclonal antibody therapies (natalizumab, alemtuzumab, rituximab), oral medications with novel mechanisms of action (fingolimod, teriflunomide, and dimethyl fumarate), and chemotherapeutic agents (cyclophosphamide and mitoxantrone). Of these, rituximab is not approved by the US FDA for use in adults with MS but its humanized version is anticipated to be approved in the Spring 2017. Safety and efficacy of these new and emerging therapies in pediatric MS is an area of intense interest. The existing safety and efficacy data have been described in several mostly retrospective studies of pediatric MS patients for some of these drugs but overall limited data are available.

Natalizumab is a monoclonal antibody targeting alpha-4 integrin, an adhesion molecule critical to immune cell migration into the brain. It achieved US FDA approval in 2004 for use in adults with MS. Its use has been described in several pediatric MS cohorts[11-15] and one small open label trial, where it has been well tolerated and effective in reducing relapse rate and progression of MS disability scores in patients with refractory disease. These off-label pediatric studies, however, are short and have not provided substantial long-term safety data in children. The most serious adverse event associated with the drug's use is the increased incidence of progressive multifocal leukoencephalopathy (PML), a possibly fatal opportunistic brain infection caused by JC virus. A manufacturer-sponsored review of all natalizumab-associated PML cases now estimates the risk of PML at 1:500 patients overall.[16] Three major risk factors were subsequently identified: 1) seropositivity for JC virus, 2) a prior history of immunosuppression, and 3) natalizumab treatment duration >12 months. Patients who have none of these risk factors may have a risk as low as 1:10,000. A patient registry and risk stratification program was recently implemented using algorithms suitable for counseling patients and their families. Notably, seropositivity for JC virus accrues at an annual rate of approximately 1%, such that at age 30 roughly a third of MS patients are seropositive for the virus.[17] This means that younger patients are more likely to fall in the low PML risk category due to their lower likelihood of prior JC virus exposure.

Fingolimod was approved by the US FDA in 2010 as the first oral agent for use in adult MS after favorable outcomes in two pivotal trials. Its unique mechanism of action modulates the sphingosine-1 receptor on T-cells resulting in their relative sequestration within lymphoid tissue. Its use has not yet been described in children. Among adult MS patients, fingolimod reduced the relapse rate as well as disability progression and was generally well-tolerated. However, several side effects have limited its extension to pediatric MS. They include lethal viral infections, cardiac arrhythmias, macular edema, liver toxicity, and reports of rebound disease activity with drug withdrawal.

Dimethyl fumaric acid was approved by the US FDA in 2013 for use in adult MS. Its use in a small group of children has been reported recently. 33% of the children did not tolerate dose escalation to the usual adolt dose of 240mg bid. Over a 15 month median treatment follow-up, 23% of the children discontinued treatment because of side effects difficult to tolerate such as GI discomfort or flushing.[18]

Teriflunomide and alemtuzumab have been approved for adult MS more recently and there are no publications on their use in children with MS. All the new medications reviewed above have in place an investigation plan in children with MS. Several clinical trials in pediatric MS are ongoing with fingolimod, teriflunomide and dimethyl fumaric acid that will clarify safety and efficacy of these drugs in young patients. Companies making drugs for which they are seeking FDA-approval also have to provide pediatric investigational plans. An international group, The Clinical Trial Task Force of the IPMSSG has started to help companies finalize investigational plans in children with MS to ensure trials are feasible within the global context of pediatric MS. Ideally, a common registry for long-term safety will be created in the future.

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