EARLY USE OF RITUXIMAB AS A FIRST LINE THERAPY IN PEDIATRIC ONSET MULTIPLE SCLEROSIS

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Abstract

Pediatric onset multiple sclerosis (POMS) is an increasingly recognized disorder with a significant morbidity. It is a challenge to select a medication for pediatric patients to maintain remission, considering the young age of onset, disease course, side effects and adherence to treatment. Here we present two cases of pediatric multiple sclerosis with a very aggressive course and who were eventually started on Rituximab as Disease Modifying Treatment (DMT). Rituximab is a safe alternative to prevent frequent relapses and can be considered as a first line disease modifying therapy in children.

Keywords:
pediatric onset MS,
Rituximab, DMT

Introduction

The incidence of pediatric MS is approximately 0.3–0.5 per 100,000 children per year with an estimated 1.7%–5.6% presenting before the age of 18 years (1). Onset of MS prior to 10 years of age is rare, occurring in only 20% of all pediatric MS patients. Over 95% of pediatric MS patients experience a relapsing–remitting disease onset with multiple episodes of CNS demyelination separated in time (more than 30 days between attacks) and involving multiple areas of the CNS (2). Patients with POMS demonstrate more inflammatory demyelination early in their disease, resulting in increased clinical relapses, rapid MRI lesion accrual, early inflammatory tissue-level injury, and, ultimately, early disability progression. Higher efficacy DMTs should therefore be considered as first line therapy to achieve full clinical remission (termed “no evidence of disease activity, or NEDA”) (3). However, the use of disease modifying drugs in developing countries is limited by their high cost and availability of these medications. We therefore review these medications along with our experience of Rituximab as a first line DMT in two prepubertal girls.

Case report

Patient I
A previously healthy, 7½ year old girl presented with history of right upper limb monoparesis along with headache and fever without altered consciousness of few day duration. Child was investigated and considered to have tuberculous meningitis based on CSF findings of lymphocytic pleocytosis and X-ray chest showing pneumonitis. She was put on 4 drug anti-Koch’s treatment (AKT) with steroids. All the symptoms abated within a few days. She later had two similar episodes within a span of 10 months of right hemiparesis along with speech changes. Possible differential diagnoses, included autoimmune vasculitis and infectious disorders were investigated. After the third event AKT was discontinued and child was considered as multiphasic ADEM based on clinical history and neuroimaging (Fig 1). Two months after the last event, she had acute onset paraparesis with incontinence of urine over a span of 3–4 days. MRI spine and brain (Fig 2) done was suggestive of pediatric multiple sclerosis according to Mc Donald criteria (4). Cerebrospinal fluid (CSF) showed a mild pleocytosis with positive oligoclonal bands which were negative in serum. Ophthalmological examination revealed right optic disc pallor and VEP showed evidence of right axonal optic neuropathy. Child was pulsed with methylprednisolone for 5 days followed by a slow taper of oral steroids. She continued to remain symptomatic even after a month on steroids. She was then transferred at our center, with an EDSS score of 9.0, where it was decided to initiate plasmapheresis as against intravenous
immunoglobulins because of economic constraints. Her neurological status improved after 3 cycles of plasmapheresis. She subsequently improved from an EDSS score of 9.0 to 3.5 at completion of plasmapheresis. Based on the history of 4 events within a period of 12 months and MRI findings, the child seemed to have an aggressive disease and it was decided to commence with disease modifying therapy. Based on the availability, cost and compliance of the treatment and the occurrence of side effects (immediate as well as long term) given that she was just 8 ½ years of age, it was decided to initiate off label treatment with rituximab (375 mg/m² intravenous on day 1 and 15) in this child. She received 1 cycle of two injections of rituximab 2 weeks apart at an interval of 6 months for period of next 2 years with no relapses till date (EDSS 2). Her recent MRI brain and spine after 2 years is given in figure 3. Previous case reports and studies (5) have documented an impressive clinical effect in a severe course of the disease.

Patient II
Another 11-year girl presented with an episode of acute onset ataxia with headache, diplopia and left hemiparesis over a span of 3 days. On investigations, CSF showed mild pleocytosis and MRI brain (Fig 4) showed ring like enhancing lesions. A differential diagnosis of abscess versus neurocysticercosis was suggested and the child was started on IV antibiotics along with steroids. Albendazole was also given for two weeks. She improved completely without any deficits over seven days. Repeat MRI brain one month later had markedly cleared; however old lesions still persisted and she was hence continued for oral antibiotics for three weeks. Few weeks later she came back with gradual onset visual loss in right eye along with ptosis and external ophthalmoplegia. She was transferred to higher center with these complaints and investigated. Ophthalmological examination suggested right optic neuritis; VEP showed right axonal optic neuropathy. CSF picture had a normal cell count; oligoclonal bands were present in CSF as well as serum. MRI brain and spine (Fig 5) revealed changes as per Mc Donald’s criteria(4). Past history revealed an episode of facial nerve palsy six months prior to her first episode treated with short course of steroids. This child was treated with intravenous methylprednisolone followed by a slow taper of oral steroids to which she responded well. Given that she had three neurological events within an eight months’ period with MRI features concordant with Mc Donald’s criteria, she too was considered as an aggressive form of the disease with EDSS 3 at presentation. Rituximab was selected as a disease modifying therapy to be administered by the same regime. She too is relapse free for a period of two years (EDSS 2). Her recent MRI brain and spine after 2 years is given in figure 6.

Discussion
Multiple sclerosis is an inflammatory demyelinating disease of the central nervous system (2) which usually begins as a relapsing, episodic disorder, evolving into neurodegenerative condition characterized by progressive neurologic disability (6). An estimated 2-5% of all individuals with MS present with symptom onset before 16 years of age (1). Present evidence (7) suggests that disease modifying therapy (DMT) should be initiated promptly following a diagnosis of MS. Various disease-modifying therapies (DMTs) used for the relapsing forms of MS (7,8,47) are noted in table 1 with their mechanism of action, benefits as well as side effects. These DMTs can be categorized as injectable, oral and infusions for the sake of discussion.

Injectable DMTs: Interferon and glatiramer acetate were one of the first FDA approved drugs for adult MS. Subsequently they were used off label in pediatric populations and have become the most studied medication in POMS. These are now considered as first line therapy for POMS (9,10). “Lateral treatment switch” is many a times recommended in case of decreased efficacy or appearance of side effects. Many studies have provided reasonable data for the use of interferon-beta and glatiramer acetate in POMS due to lack of short-term complications and safety (11-15). However, the major disadvantage of these medications are their frequent injections on monthly to daily basis- a practice generally avoided in pediatric medicine. In a large retrospective study of children in the US, approximately 1/5 of children on IFN and GA discontinued these therapies due to poor tolerance or compliance, and over 1/4 changed therapies due to breakthrough disease (16).
Oral DMTs: The new orally administered drugs approved for MS treatment show significant therapeutic advances. These include fingolimod (17,18), dimethyl fumarate (19,49) and teriflunomide (45) along with cladribine and laquinimod (phase III trials) (20). Fingolimod has now received approval as Breakthrough Therapy designation for pediatric MS (21). Their use in pediatrics as an off-label treatment has very limited data on its efficacy and safety (22). Further studies are required to assess their long term safety and efficacy. Azathioprine, methotrexate and mycophenolate mofetil are some other drugs which have shown benefit in various case studies (23,24, 48) from resource poor settings.

Infusion DMTs: This group of DMTs include use of new biologicals such as rituximab and natalizumab. Rituximab is fast emerging as a preferred drug modifying therapy owing to its efficacy, safety (25) as well as tolerability in pediatric population (26). Many child neurologists are even advocating use of rituximab as a first line therapy in POMS (27). It is easy to administer and has no long term side effects proven till date. Natalizumab is another recombinant, humanized monoclonal antibody used off label in POMS. Recent case series have reported good efficacy and tolerability in children (28,29). However, known risk of PML and its cost is a major hindrance for its use in developing economies (30). Cyclophosphamide has been shown to be effective in relapse rate reduction and in control of MRI lesion accrual but has variable effects in delaying disease progression (31,32,33). Though very cost efficient as compared with other infusions, it is associated with a lot of side effects such as vomiting, transient alopecia, osteoporosis, and amenorrhea which needs to be carefully monitored in post pubertal girls and boys. Mitoxantrone has been considered for treatment of refractory MS for a long time now (34,35,36). Though it has easy application, simple monitoring and very low cost, it needs to be balanced against its toxicity and long term risk of cardiotoxicity and leukemia which are very important considering the age of our patients.

Choosing the drug for Pediatric Patient in India
All drugs are currently available in India. As most of them have no clinical trials for pediatric patients, it is on the treating child neurologist to decide on the treatment strategy. The exorbitant cost of DMTs however makes it unaffordable to clear majority of pediatric patients with MS in resource poor countries such as India. The current cost of these drugs in India is shown in table 2. This decision has to be optimized based on clinical status of the child, long term side effects and functional disability and most importantly compliance and adherence to treatment. The patient and family should be engaged in the choice of therapy, keeping in mind long term cost, additional financial burden of disability, possible side effects in young children, proximity to a medical center capable of managing acute events, as this is likely to promote adherence to treatment. In our cases, all these factors were considered and a consensus was reached to treat both these pre-pubertal girls with Rituximab for a total of 4 cycles. At the end of the treatment and now two years after the completion of treatment, there have been no relapses or new lesions on MRI brain. Both girls have tolerated the drug very well and did not show any side effects- short term or long term. They are not on any other form of immunosuppression. We therefore would like to recommend use of Rituximab infusion as first line therapy for POMS like in adults.

Conclusions
Pediatric onset multiple sclerosis is increasingly recognized and has a significant morbidity. It provides a huge financial burden of disability on the families more so in patients of poor economic strata. Choice of DMT must be made keeping in mind the availability and cost of drugs along with economic conditions of the families to improve adherence to the treatment.

References
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19. Ian Rossman, Manikum Moodley, Mary Rensel Dimethyl Fumarate Is Well Tolerated in a Small Cohort of Pediatric-Onset Multiple Sclerosis Patients (P3.010) Neurology Apr 2016, 86 (16 Supplement)

Table 1 Drug Modifying treatments

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Dose</th>
<th>Reduction in relapse rates</th>
<th>Side Effects</th>
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<tbody>
<tr>
<td>IFNB1b</td>
<td>Binds to receptors on cell surface resulting in transcription regulation to decrease peripheral interferon gamma and cytokine production</td>
<td>250 mcg SC alternate day</td>
<td>34% reduction in relapse rates at 2 years; MRI load reduced</td>
<td>Infections, Sinusitis, Risk of CJD</td>
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<tr>
<td>IFNB1a</td>
<td>Impedes entry of activated T-cells into the CNS. (37)</td>
<td>44 mcg SC thrice weekly</td>
<td>33% reduction in relapse rates at 2 years; MRI load reduced</td>
<td>Abscess at injection sites</td>
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<tr>
<td>Glatiramer acetate</td>
<td>Regulates T cell response by altering antigen presenting cells (38)</td>
<td>20 mg SC daily</td>
<td>29% reduction in relapse rates at 2 years</td>
<td>Bronchitis, cystitis, pyelonephritis, Herpes simplex</td>
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<tr>
<td>Mitoxantrone</td>
<td>Suppresses the proliferation of T cells, B cells, and macrophages Impairs antigen presentation and decreases the secretion of proinflammatory cytokines Enhances T-cell suppressor function and inhibits B-cell function and antibody production Inhibits macrophage-mediated myelin degradation. (39)</td>
<td>12 mg/m² IV every 3 months</td>
<td>66% reduction</td>
<td>Infections, cancers, cardiotoxicity</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Suppresses IL-12 and Th1-type responses and enhancing Th2/Th3 responses (40)</td>
<td>600-1000mg/m² monthly for a year</td>
<td>60-70% reduction</td>
<td>Interstitial pneumonia, hemorrhagic cystitis, alopecia, infertility</td>
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<tr>
<td>Rituximab</td>
<td>Monoclonal antibody targeting the CD20 receptor on activated B cells. (41,42)</td>
<td>375 mg/m² IV twice in 4 weeks</td>
<td>50% reduction in relapse rates</td>
<td>PM, infections, hematological conditions</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Monoclonal antibody that targets integrin molecules on the vascular endothelium of the blood brain barrier.</td>
<td>300 mg IV once monthly</td>
<td>68% reduction in relapse rates</td>
<td>Opportunistic infections, encephalitis, UTI</td>
</tr>
<tr>
<td>Agent</td>
<td>Cost per month in INR</td>
<td>Cost for 1 year in INR (US$)</td>
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<tr>
<td>IFNB 1b</td>
<td>Rs. 70,000 – Rs. 75,000</td>
<td>Rs. 8 lacs – Rs. 9 lacs</td>
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<tr>
<td>IFN 1a</td>
<td>Rs. 20,000 – Rs. 30,000</td>
<td>Rs. 2 lacs - Rs. 3 lacs</td>
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<td>Glatiramer acetate</td>
<td>Rs. 25,000– Rs. 35,000</td>
<td>Rs. 3 lacs - 4 lacs</td>
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<tr>
<td>Mitoxantrone</td>
<td>Rs. 333 – Rs. 450</td>
<td>Rs. 4,000 – Rs. 5,000</td>
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<tr>
<td>Cyclophosphamide</td>
<td>Rs. 5000– Rs. 6000</td>
<td>Rs. 60,000 –Rs. 70,000</td>
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<td>Azathioprine</td>
<td>Rs. 500- Rs. 600</td>
<td>Rs. 6000- Rs. 8000</td>
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<td>Rituximab</td>
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<td>Rs. 80,000 – Rs. 1 lac</td>
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<td>Natalizumab</td>
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<td>Fingolimod</td>
<td>Rs. 1500</td>
<td>Rs. 18000</td>
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<tr>
<td>Teriflunomide</td>
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<tr>
<td>Dimethyl fumarate</td>
<td>Rs. 60000</td>
<td>Rs. 720000</td>
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Table 2 Cost of DMT

Preventing migration of T and B cells. (43)

Fingolimod Modulates spingosine-1-phosphate receptors and retains autoreactive lymphocytes in the lymph node (44)

0.25- 0.5 mg once a day oral

Still in clinical trials

Leucopenia, seizures/epilepsy, allergies

Teriflunomide inhibits mitochondrial enzyme for DNA replication, reducing activation and proliferation of T and B-cells. (45)

7 mg once a day oral

Still in clinical trials

diarrhea, nausea, hair thinning, and increased alanine aminotransferase levels

Dimethyl fumarate

Probable cytokine production and lymphocyte count (46)

240 mg twice daily oral

Tolerated well

GI upset, flushing

Azathioprine

Antagonizes purine metabolism and may inhibit synthesis of DNA, RNA, and proteins.

3 mg/kg/day orally daily

30-40% reduction

OI, malignancies
Figure 1: Focal areas of hyperintensities on FLAIR images seen in bilateral periventricular white matter, centrum semiovale, corona radiata and corpus callosum. There is heterogeneous FLAIR hyperintense lesion seen in left parietal subcortical white matter likely to be tumefactive demyelination which was reported as Tubercular meningitis.

Figure 2: Extensive FLAIR and T2 hyperintense nodular lesions in bilateral periventricular deep white matter, fronto-parieto-temporo-occipital subcortical white matter along with lesions in corpus callosum. Long segment T2 hyperintense lesion is seen over cervico-dorsal cord from C2 to D12 vertebral level. There is decrease in size of previously seen tumefactive demyelinating lesion.
Figure 3 No fresh plaque or lesion in brain and spinal cord. Extensive lesions seen in earlier scans have decreased. Focal area of gliosis is noted over left parietal subcortical white matter.

Figure 4 Two ring enhancing lesions are noted over right frontal and parietal region. Multiple areas of FLAIR hyperintensities noted over bilateral periventricular regions.
Figure 5 Partial resolution of previously noted ring enhancing FLAIR hyperintense lesion over right frontal region noted. Multiple FLAIR hyperintensities are noted in bilateral centrum semiovale with subtle peripheral enhancement. Long segment T2 Hyperintensities noted over entire cervical cord.

Figure 6 There is significant reduction in previously noted bilateral FLAIR hyperintense as well as contrast enhancing lesions with few FLAIR hyperintense lesions over centrum semiovale and corpus callosum noted. There is significant resolution of lesion noted over cervical spinal cord.