Insights on Chronic-Relapsing Opsoclonus-Myoclonus From a Pilot Study of Mycophenolate Mofetil

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Opsoclonus-myoclonus syndrome is characterized by abnormal lymphocyte trafficking into brain. The authors hypothesized that mycophenolate mofetil, a lymphocyte proliferation inhibitor, might be therapeutic. The cerebrospinal fluid and blood immunophenotypes of 15 children with predominantly chronic-relapsing opsoclonus-myoclonus syndrome were compared before and after treatment by flow cytometry. Mycophenolate mofetil reduced the cerebrospinal fluid expansion of HLA-DR+ activated T cells (−40%); the frequency of other T-cell or natural killer cell subsets remained unchanged, but cerebrospinal fluid B cells increased significantly. Adrenocorticotropic hormone dose was lowered by 64% over an average of 1.5 years, yet 73%

eventually relapsed despite therapeutic drug levels. Prior treatment with rituximab prevented relapse-associated increase in cerebrospinal fluid B cells, without hindering mycophenolate mofetil–induced reduction in T-cell activation. These data demonstrate resistant immunologic problems in chronic-relapsing opsoclonus-myoclonus syndrome. Mycophenolate mofetil did not prevent relapse. The novel effect of mycophenolate mofetil on chronically activated T cells may contribute to its efficacy in T-cell mediated neurological disorders.

Keywords: cerebrospinal fluid immunophenotyping; Kinsbourne syndrome; neuroblastoma; paraneoplastic syndrome

ycophenolate mofetil was marketed in the United States in 1995 to prevent organ transplant rejection. For that indication, it was found to be

primarily a prophylactic, not first-line agent. More recently, it has been applied to inflammatory conditions in adults and children, and can be used adjunctively with other immunotherapies.[1-4] Mycophenolate is a "pluripotent immunomodulator," inhibiting proliferation of B and T lymphocytes, antibody production of polyclonal activated B cells, and formation of vascular adhesion molecules, and altering cytokine secretion.[5] Its safety profile is well suited to long-term immunosuppression.[1,5]

Experience with mycophenolate mofetil in neuroimmunological disorders suggests some patients may benefit. Controlled trials found improvement in myasthenia gravis[6] but not multifocal motor neuropathy.[7] Varying results of mycophenolate use in dermatomyositis,[8] chronic immune demyelinating polyneuropathy,[9] multiple sclerosis,[4] and Guillain-Barré syndrome[10] have been reported in small case series or retrospective reviews. Most of these trials have been in adults and entailed adjunctive therapy at doses lower than required to prevent transplant rejection.

Opsoclonus-myoclonus syndrome is an autoimmune movement disorder, characterized by abnormal trafficking of B and T cells into the central nervous system.[11,12] Conventional immunotherapies are routine,[13] but do not prevent relapse triggered by weaning or illness, which occurs

in 52% to 68% of cases.[14,15] In the chronic-relapsing form of opsoclonus-myoclonus syndrome, children are dependent on immunotherapy for years and still sustain wide-ranging neuropsychiatric sequelae, from ataxia and language impairment to behavioral disorders and mental retardation.[14] Some exhibit signs of progressive encephalopathy, with declining cognitive scores.[16]

Chronic-relapsing opsoclonus-myoclonus presents an especially difficult therapeutic challenge, because the underlying immunological mechanisms have not been elucidated. Whether chronic-relapsing disease merely represents a failure to contain and extinguish the initial onslaught of autoimmune inflammation or it stems from discrete multiphasic immunologic attacks remains an important area of research. The relative contribution of B and T cells in relapse is unclear, with good arguments being made for either or both. B-cell involvement in auto-immune disease may be T-cell dependent, for instance, or T-cell independent.[13] Empiric approaches, such as the combination of cyclophosphamide with dexamethasone pulses,[17] indicate that some children still respond to aggressive immunotherapy, but there have been no strategies to tease out immune mechanisms.

We hypothesized that a drug decreasing lymphocyte proliferation might be helpful in maintaining remission. There have been no publications on mycophenolate mofetil in opsoclonus-myoclonus syndrome besides the 12 cases we reported in abstract form, which are included here.[18]

We now describe preliminary experience with open-label, primarily add-on mycophenolate mofetil for chronic-relapsing opsoclonus-myoclonus syndrome in a convenience sample.

In this study, a subgroup of children had been treated previously with rituximab, an anti-CD20 monoclonal antibody. The rationale for the use of rituximab is its selective targeting of circulating B cells. Rituximab very effectively eradicates cerebrospinal fluid B cells in opsoclonus-myoclonus syndrome for at least 6 to 12 months after treatment in most patients.[19,20] There are 22 reported cases of clinical benefit.[19,20-22] Because both B-lymphocyte and T-lymphocyte phenotypic abnormalities occur in opsoclonus-myoclonus syndrome, we hypothesized that the tandem combination of rituximab and mycophenolate mofetil might be more effective than mycophenolate mofetil alone.

Participants and Methods

Participants

A total of 19 children with opsoclonus-myoclonus syndrome were recruited to the National Pediatric Myoclonus Center and parents signed informed consent for this Institutional Review Board–approved protocol. Their clinical characteristics were as follows: 87% chronic, previously treated; 93% with history of relapse; 73% mild; mean age 4.7 ± 0.7 (SEM) years; 47% boys; 60% neuroblastoma, all resected; 10 co-treated with adrenocorticotropic hormone (ACTH), intravenous immunoglobulin (IVIg), or dexamethasone; 7 previously treated with rituximab within 6 to 12 months; no vaccinations for at least 2 years before or during treatment. Each child underwent a clinical evaluation, videotaping, and a lumbar puncture at initial evaluation and 0.8 ± 0.3 years (range 0.5-3.2) after initiation of mycophenolate mofetil. Because most of the cases were mild, the primary end points were the cerebrospinal fluid immunophenotype and relapse, not clinical improvement.

Drug Administration and Monitoring

Mycophenolate mofetil (Cellcept, Roche Pharmaceuticals, Nutley, NJ) was started at 600 mg/m^2 in 2 divided doses as oral suspension (200 mg/mL). Parents were instructed to give the drug on an empty stomach: 1 hour before breakfast, 2 hours after dinner (no food for another hour).

Trough serum levels of mycophenolic acid (the active immunosuppressant) and mycophenolic acid 7-O-glucuronide (largely inactive metabolite), as well as complete blood counts, were obtained at intervals. Mycophenolic acid and its 7-O-glucuronide derivative were measured by high-pressure liquid chromatography at National Medical Service (Willow Grove, Pa) through Specialty Lab (Santa Monica, Calif). Mycophenolate mofetil dose was titrated to achieve a high therapeutic level when possible. Mycophenolate mofetil was discontinued soon after starting it in 4 children with intolerance to the bitter taste (despite containing aspartame), intermittent vomiting, or negligible blood level; 15 patients continued the study.

In the previously rituximab-treated subgroup (n = 7), rituximab had been given as 375 mg/m^2 intravenously (IV) on each of 4 consecutive weeks. The time elapsed between rituximab and mycophenolate mofetil treatment was 1.2 ± 0.9 years (SD) (ranges 0.6-3).

Lymphocyte Phenotyping

Using published methods,[11,12] expression of lymphocyte surface antigens was investigated with a comprehensive panel of directly conjugated monoclonal antibodies to adhesion and activation proteins in combination with anti-CD3 and anti-CD45 antibodies. All samples were acquired and analyzed on a dual-laser fluorescence activated cell sorter (FACS) Caliber cytometer (Becton-Dickinson, San Jose, Calif). Data acquisition and analysis were performed with CellQuest (Becton-Dickinson). Dependent on surface marker fluorochrome, data were plotted as log versus log of fluorescence. Quality control was maintained as described previously.[12] Pediatric control data for the cerebrospinal fluid immunophenotype (immunotherapy-naïve children with nonimmunologic neurological disorders) and blood immunophenotype

Table 1. Relapse Data

Variables	All Patients (n = 15)	Rituximab pretreated (n = 7)	No Rituximab (n = 8)
Relapsers (n)	11 (73%)	4 (57%)	7 (88%)
Time after mycophenolate mofetil to relapse (years)	1.0 ± 0.3 (0.08-2.4)	0.8 ± 0.5 (0.08-2.2)	1.1 ± 0.3 (0.33-2.4)
Total time on mycophenolate mofetil (years)	1.5 ± 0.3 (0.5-3.7)	1.2 ± 0.2 (0.62-2.1)	1.7 ± 0.4 (0.5-3.7)
Duration of follow-up (years) (2.1-6.1)	3.6 ± 0.4 (2.1-3.5)	2.8 ± 0.2 (2.4-6.1)	4.4 ± 0.6
Relapse triggers (n)			
Immunotherapy tapering or discontinuation	6	1	5
Illness	4	3	1
Unknown	1	0	1
Relapse frequency (n)			
One relapse	9	4	5
Two relapses	1	0	1
Three relapses	1	0	1
Relapse severity (n)			
Mild	5	3	2
Moderate	6	1	5
Severe	0	0	0

Data are means ± SEM or frequencies. Ranges are given in parentheses. Frequency data were analyzed by Fisher exact test. The relapse rate, which was comparably high in both treatment groups, did not differ significantly between groups. The duration of follow-up for the rituximab-pretreated mycophenolate mofetil group was slightly shorter than for the no rituximab group ($P = .03$, 2-tailed t test).

(neurological controls and healthy children) have been published previously.[12,23,24]

Scoring of Neurological Status

A trained observer, blinded to treatment status, rated videotapes using the Opsoclonus-Myoclonus Syndrome Evaluation Scale (12-item motor scale was scored in increasing severity from 0 to 3).[12] Subscores were converted to a total score.

The term relapse was used to indicate a distinct worsening or return of neurological symptoms or signs lasting more than 24 hours. Relapse reporting was based on questioning the parents at the time of the relapse. Relapse severity was designated as mild in the presence of slight imbalance or tremulousness, moderate if opsoclonus was also present but the patient was still ambulatory, and severe if patient was nonambulatory.

Data Analysis

Statistical analysis was performed using Microsoft Excel and SPSS (SPSS, Inc, Chicago, Illinois). Means of independent groups were analyzed by 2-tailed t tests; pretreatment and post-treatment means by paired t tests. The level of significance was $P < .05$. Frequency analysis was done by Fisher exact test.

Results

Clinical Response

The mean trough serum concentration of mycophenolic acid was 2.6 ± 0.4 μg/mL (therapeutic range, 1.0-3.5), and the mean mycophenolate mofetil dose was 820 ± 73 mg/m²/day (range, 108-1187). Mycophenolic acid

7-O-glucuronide concentration was 20 ± 3 μg/mL (reference range, 35-100). Mycophenolic acid level and mycophenolate mofetil dose were not correlated. Absolute lymphocyte count (3.1 ± 0.3 K/mm³) and other leukocyte and erythrocyte blood counts were normal.

On mycophenolate mofetil for an average of 1.5 years, the dose of ACTH was reduced by 64% ± 12% (range, 0-100) from 61 ± 23 IU/m² to 11.8 ± 2.76 IU/m² ($P = .055$, paired t test). The child chronically co-treated with dexamethasone underwent dose reduction from 3 to 0.2 mg, his lowest dose. Adrenocorticotropic hormone and mycophenolate mofetil doses were not correlated. However, mean total motor score did not change (9.9 ± 2.0, 8.5 ± 1.2); it decreased by 5% to 76% in 6 children.

Relapse information was gathered on all patients (Table 1). Pretreatment total score was not significantly higher statistically in subsequent relapsers (11.2 ± 2.5) than nonrelapsers (6.5 ± 2.1; $P = .31$). After mycophenolate mofetil, total score was not significantly different in relapsers (9.0 ± 1.6) and nonrelapsers (7.3 ± 1.2). Mean mycophenolic acid concentration (μg/mL) was therapeutic in relapsers (2.5 ± 0.4) and in nonrelapsers (2.7 ± 0.9).

In rituximab-pretreated patients, all but 1 relapse was caused by illness, not immunotherapy tapering, and none had multiple relapses. The group had a lower relapse frequency, but the difference was not statistically significant.

Seven of the eight patients not treated previously with rituximab had a prior history of relapse (3 with a single relapse, 2 with 2 relapses, 2 with 4 or more relapses), and all but 1 relapsed on mycophenolate mofetil. The 8 patients are now off mycophenolate mofetil and 5 have not required new treatments. The other 3 were subsequently treated with rituximab; 2 of them remain on IVIg or ACTH.

Table 2. Effect of Mycophenolate Mofetil Treatment on Cerebrospinal Fluid Immunophenotype

Cell Type	Monoclonal Antibody Labeling	Premycophenolate Mofetil	Postmycophenolate Mofetil
Total T cells	CD3+	83 ± 3.0	86 ± 1.4
T helper/inducer	CD3+CD4+	49 ± 3.9	56 ± 3.3
T cytotoxic/suppressor	CD3+CD8+	31 ± 3.2	27 ± 1.7
γδ T cells	CD3+TCR γδ+	7.8 ± 2.0	7.1 ± 1.3
NKT cells	CD3+CD16,56+	3.3 ± 0.7	4.7 ± 0.94
NK cells	CD3-CD16,56+	7.7 ± 2.6	4.9 ± 0.74
Naïve T cells	CD3+CD45RA+	13 ± 2.1	21 ± 6.4
Memory T cells	CD3+CD45RO-	66 ± 5.7	74 ± 2.5
Acutely activated T cells	CD3+CD25+	8.7 ± 1.8	6.5 ± 1.1
Chronically activated T cells	CD3+HLA-DR+	30 ± 3.7	17 ± 1.7[a]
Total B cells	CD3-CD19+	0.58 ± 0.17	1.8 ± 0.46[b]

Note: NKT, natural killer T; TCR, T-cell receptor.
a. $P = .0007$, [b] $P = .014$, paired t tests. Data are cell percentage means ± SEM. There were no other statistically significant differences. In controls, the frequencies were 0.76% ± 0.24% for B cells and 14.5% ± 1.7% for chronically activated T cells.

Cerebrospinal Fluid Immunophenotype

Prior to mycophenolate mofetil, children exhibited the lymphocyte subset frequency abnormalities we found previously: expanded CD19 + B cells, chronically and acutely activated T cells, cytotoxic/suppressor T cells, and a low helper/suppressor T-cell ratio.

Mycophenolate mofetil significantly reduced the relative size of the chronically activated T-cell subset in cerebrospinal fluid (Table 2). It lowered the percentage of chronically activated T cells, previously 2-fold above controls, by 44% (range 0%-64%) to control levels (Figure 1A). Prior treatment with rituximab did not prevent the mycophenolate mofetil–induced reduction in the frequency of chronically activated T cells (Figure 1B). The percentage of HLA-DR+ T cells did not differ significantly between ACTH co-treatment and those not on ACTH (data not shown).

Mycophenolate mofetil had no significant effects on the percentage of cerebrospinal fluid total T cells, T-helper/suppressor T cells, T-cytotoxic/suppressor cells, natural killer–like T cells, natural killer cells, or γδ T-cells.

Before mycophenolate mofetil, the mean percentage of cerebrospinal fluid B cells in opsoclonus-myoclonus syndrome did not differ from controls (< 1%). Afterward, there was a significant 3.1-fold increase due to a subgroup with relapse. All relapsers exhibited cerebrospinal fluid B-cell expansion ($P = .032$) at reevaluation (Figure 2); 3 had the highest B-cell percentages (5.4%, 5.1%, 3.6%). Compared to the pretreatment evaluation (0.66% ± 0.2% B cells), the frequency of cerebrospinal fluid B cells was 3.3-fold higher at relapse (2.2% ± 0.6%). Pretreatment with rituximab prevented cerebrospinal fluid B-cell expansion during mycophenolate mofetil treatment.

Blood Immunophenotype

Mycophenolate mofetil had no statistically significant effect on the blood lymphocyte phenotype, which was
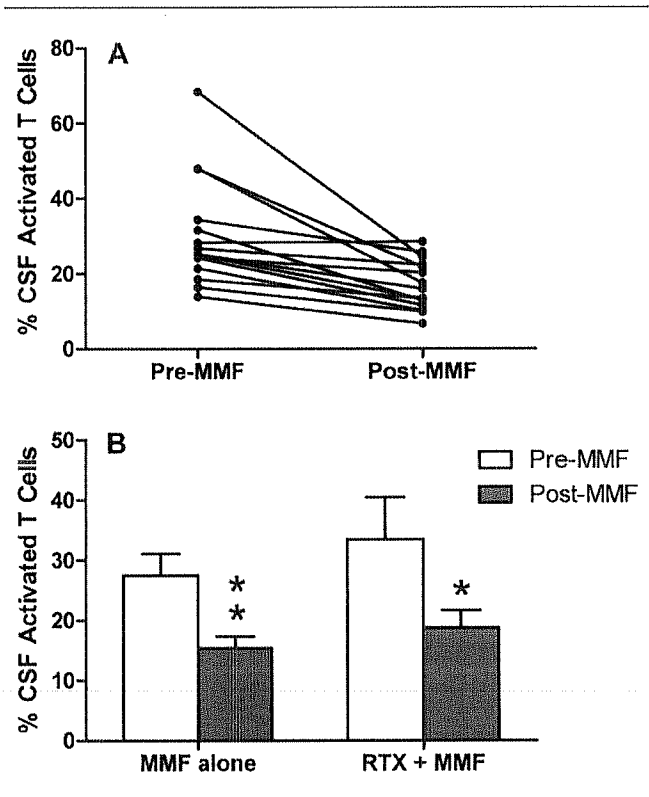

Figure 1. Effect of mycophenolate mofetil (MMF) on (A) the frequency of cerebrospinal fluid (CSF) chronically activated T cells in individual patients and (B) subgroups with or without rituximab (RTX) pretreatment. Data are means ± SEM. Statistical comparisons were made pretreatment and posttreatment by paired t tests: $*P = .043$, $**P = .0059$.

therefore not predictive of the drug's central effects. The percentage of chronically activated T cells (2.3% ± 0.4% pretreatment, 2.1% ± 0.4% posttreatment) and their cerebrospinal fluid/blood ratio (pretreatment 15.4 ± 2.8, posttreatment 11.0 ± 1.9) were not significantly altered by mycophenolate mofetil.
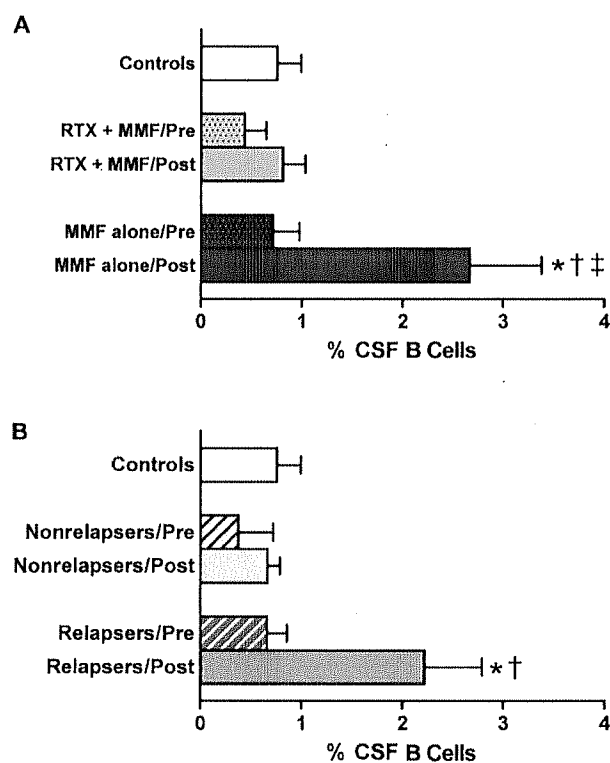
A

B

Figure 2. A, Comparative effect of mycophenolate mofetil on the frequency of cerebrospinal fluid (CSF) B cells in patients with or without rituximab pretreatment. Data are means ± SEM. The increase in B cells during mycophenolate mofetil treatment is due to the subgroup of children who received mycophenolate mofetil without rituximab (mycophenolate mofetil alone/post). Paired *t* tests were used for statistical comparisons of premycophenolate mofetil and postmycophenolate mofetil data (*) and 2-tailed *t* tests were used to make comparisons with controls (†) or between posttreatment groups (‡): *P = .023, †P = .0069, ‡P = .037. B, Effect of relapse on cerebrospinal fluid B-cell frequency. Postmycophenolate mofetil, the percentage of cerebrospinal fluid B cells was increased only in relapsers. *P = .018, †P = .021. MMF = mycophenolate mofetil; RTX = rituximab.

Discussion

We found no previous literature concerning the effect of mycophenolate mofetil on human cerebrospinal fluid lymphocyte subsets in vivo. The reduction in frequency of chronically activated T cells is of broad clinical interest, due to increased T-cell activation in multiple sclerosis, paraneoplastic cerebellar degeneration, and other autoimmune neurological disorders.[25] It may be relevant to the putative efficacy of mycophenolate mofetil in various neuroimmunological disorders.[5] Mycophenolate mofetil also affects cell types not studied here, such as monocyte-derived dendritic cells and microglia.[26,27]

Although mycophenolate mofetil has inhibitory effects on B-cell production of immunoglobulins and cytokines in vitro,[28] 33% of children treated with mycophenolate

mofetil developed cerebrospinal fluid B-cell expansion. Because the relapse rate in opsoclonus-myoclonus syndrome is high and we are not aware of a mechanism to link mycophenolate mofetil directly to B-cell expansion, we surmise that inherent immune dysregulation in opsoclonus-myoclonus syndrome was the reason for B-cell expansion. Both cerebrospinal fluid B-cell expansion and reduction in the percentage of cerebrospinal fluid CD4+ T cells correlate with motor severity in opsoclonus-myoclonus syndrome.[12] Prior treatment with the anti-B-cell monoclonal antibody rituximab[20] reduced the likelihood of relapse without abrogating mycophenolate mofetil–induced reduction in cerebrospinal fluid–activated T-cell frequency. These data strengthen the argument for the role of B cells in relapse, but a necessarily larger study of immunological mechanisms of relapse is under way at our center.

Failure of mycophenolate mofetil to alter the cerebrospinal fluid T-cell phenotype, except for expression of the chronic T-cell activation marker HLA-DR, does not exonerate the T-cell in opsoclonus-myoclonus syndrome. Studies of lymphocyte function and cytokine production need to be done. The possibility and potential clinical benefit of using different methods to manipulate cerebrospinal fluid T cells and other cells, especially early in the course of the disease, remains intriguing.

The pediatric pharmacokinetic data provided by this study should be helpful to the clinician. Monitoring mycophenolic acid concentration, though controversial,[29,30] was useful to us in guiding mycophenolate mofetil dosing due to substantial interindividual and intraindividual variability.[4,31] In children with autoimmune vasculitis, effective therapy occurred at 900 ± 341 mg/m²/day and mean trough mycophenolic acid concentration of 3.1 ± 1.1 µg/mL.[2] Higher drug levels can be tolerated as long as the mycophenolic acid level is < 5 µg/mL, due to increased risk of immunosuppression, not drug toxicity. Even so, 3 to 9 months must be allowed for mycophenolate mofetil to exert clinically beneficial immunologic effects.[5] Mycophenolate mofetil was easier to use once parents understood that food impaired absorption and accounted for subtherapeutic levels, yet 19% of children did not tolerate its taste or could not be stopped from snacking. As found in other studies, side effects were few,[2] and there was no increase in serious or opportunistic infections.

Initially, we thought that mycophenolate mofetil might be a "steroid sparer" in opsoclonus-myoclonus syndrome.[18] However, given the high relapse rate over longer term follow-up, steroid-sparing begs the question. It is clinical practice to taper corticosteroids or ACTH anyway until they are no longer needed or there is relapse. This issue has hampered the evaluation of adjunctive immunosuppressants, including mycophenolate mofetil, in corticosteroid-responsive autoimmune disorders.[5] Only

a conventional therapy opsoclonus-myoclonus syndrome group, matched carefully for immunological as well as clinical severity, steroid doses, and taper rates, could provide an adequate control, but such a group would not be medically advised.

In summary, the performance of mycophenolate mofetil in chronic-relapsing opsoclonus-myoclonus syndrome was disappointing. The study did serve to identify some potential immunological mechanisms of relapse, and emphasizes the need for effective front-end therapies, before the disease becomes chronic and treatment resistant. Mycophenolate mofetil effects on T cells are highly relevant to T-cell mediated neurological disorders.

Acknowledgments

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