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Mycophenolate Mofetil, a Possible Therapeutic Agent for Children with Juvenile Dermatomyositis

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Abstract

Objective—To determine if mycophenolate mofetil (MMF) diminished skin and muscle disease activity in children with juvenile dermatomyositis (JDM) permitting decrease in corticosteroid dosage.

Methods—Retrospective data review for 50 JDM children identified the following: 38 (76%) girls, 39 (78%) white, 10 (20%) Hispanic, 1 (2%) black, mean age 12.2 ± 5.0 years who had been given MMF for 12 months. MMF dose and frequency, type of infection, white blood cell count (WBC), corticosteroid dose and validated disease activity score (DAS), (sub scores for skin [DAS-S], muscle [DAS-M]), were obtained.

Results—Twelve months after start of MMF, mean DAS-S decreased from 5.24 ± 0.29 to 3.72 ± 0.29 (p=0.001) and DAS-M dropped from 2.44 ± 0.39 to 1.17 ± 0.28 (p=0.002). Prednisone dose decreased from 0.39 mg/kg/day ± 0.06 mg to 0.23mg/kg/day ± 0.02 mg (p=0.0001), with resumption of linear growth (p=0.008). The WBC/lymphocyte count was unchanged over 12 months on MMF. Infection rate was assessed in a subset of 26 children with JDM followed for 12 months *before* start of MMF and compared with ensuing 12 months on MMF. There was no significant difference between pretreatment and first 6 months of MMF (p=0.44), but infection rate dropped in months 7–12 (p=0.001).

Conclusions—MMF appears to be worthy of consideration as an additional therapeutic modality for treatment of children with JDM. These data suggest that use of MMF decreases skin and muscle disease activity and is steroid sparing. MMF appears to be well tolerated, but patients should be monitored for infection.

Juvenile dermatomyositis (JDM) is the most common pediatric inflammatory myopathy, with an incidence of 3.2 cases/million children/year in the US (1). Children present with a characteristic rash, which includes heliotrope discoloration of the eyelids and Gottron's papules on extensor surfaces, and symmetrical proximal muscle weakness. The primary lesion in JDM is a systemic small vessel vasculopathy (2), which visibly progresses with delay in the institution of effective immunosuppressive therapy (3), and is reflected in gene expression profiles of muscle from untreated children with definite/probable diagnosis of

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JDM (4). Gene expression profiles of muscle (5,6,7) as well as peripheral blood from adults (8,9) and children (10) with dermatomyositis have also demonstrated up-regulation of Type-1 interferon (IFN)-inducible genes, as well as increased interferon-alpha (IFN-α) activity in sera of untreated children with JDM (11). The gene expression profiles from children with JDM share features with gene expression profiles obtained from examination of blood from patients with lupus (12). Although distinct clinical entities, some of the commonality of gene expression suggests there may be similarities in the pathophysiology between these diseases and that treatment modalities may overlap as well.

The specific approach to therapy for JDM is controversial, but corticosteroids are the cornerstone of treatment (13). The numerous side effects of corticosteroids, particularly the negative impact on growth in children, as well as lack of adequate clinical response to this regimen in some patients, has prompted a search for alternative immunosuppressant therapy for children with active symptoms of JDM. Mycophenolate mofetil (MMF) is established as an effective treatment for lupus nephritis and other systemic lupus manifestations in both adults (14) and children (15). Furthermore, adult dermatomyositis patients were reported to have symptomatic improvement with MMF therapy (16,17). Initially approved for the prevention of organ transplantation rejection, (18) MMF has been employed in the management of a range of other autoimmune diseases (19).

The mechanism of action of MMF has been studied and has shown that hepatic metabolism converts MMF to the active moiety, mycophenolic acid (MPA). MPA selectively inhibits de novo purine metabolism by reversibly binding to inosine monophosphate dehydrogenase. By depleting guanosine and deoxyguanosine nucleotides in T and B lymphocytes, it inhibits their proliferation, antibody production, and prevents leukocyte binding to endothelial cells (20). Our experience of the response of children with JDM to MMF was assessed by comparing clinical and laboratory information at the time of start of MMF therapy with that at the 6 and 12 month follow-up visits.

PATIENTS AND METHODS

Patients

The medical records of all children diagnosed with definite/probable JDM at Children's Memorial Hospital Pediatric Rheumatology clinic were reviewed. Children with overlap syndrome were excluded. We included all patients in this retrospective analysis who had received MMF for a minimum of 12 months, n=50. The Institutional Review Board approved this study (IRB #2002–11762).

Indications for use of MMF

The major indication for the addition of MMF to the therapeutic regimen was lack of the child's response to previous interventions. This is documented in Table 1 as duration from onset of symptoms to start of MMF, mean 3.6 (range 0.2–16.2) years, as well as duration of symptoms from onset of first symptom to initial treatment, mean 2.8 years (range 0.1–15.2). Children with JDM who had already been treated, 32/50, were referred from other centers, and they had a much more varied background of previous therapy. After evaluation, the initial therapy at our center is fairly standard and was used in 46/50 (92%) patients, under the direction of a single physician (LMP). IVMP at 30 mg/kg, was administered daily on three consecutive days when possible, followed by IVMP given once to three times a week, with oral prednisone at 0.5 mg/kilo on non-IVMP days, until the child's indicators of immune activation had normalized. In addition, the following was used: methotrexate at a minimum of 15 mg/meter square, vitamin D to achieve a blood level in the therapeutic range (>35ng/mL), 1 gm of folic acid and a proton pump inhibitor. Hydroxychloroquine was also

administered on a less consistent basis and usage of sunscreen with a minimum of SPF 40 was urged. In the remaining four untreated patients with a severe rash at presentation, MMF was begun as part of the initial therapy.

Assessments

MMF effectiveness was assessed by comparing clinical and laboratory information at the time of start of MMF therapy with that at the 6 and 12 month follow-up visits. All eligible patients who had been followed for at least 12 months were included in the analyses. For analysis of the infection rate, the number and type of infections occurring in 26/50 patients followed by our clinic for the 12 months before the start of MMF therapy was compared with the number and type of infections in the 12 months after MMF had been initiated.

Validated DAS (21), including skin and muscle involvement subscores, were calculated for patients at onset and follow-up visits. All JDM patients were started on an initial dose of 20mg/kg of MMF divided twice a day. Data on MMF dosing and adverse events attributed to MMF, including types of infection and frequency, were obtained. Additional medications prescribed for JDM, including corticosteroid dose and frequency, were recorded at start of MMF therapy and at 6 and 12 month follow-up visits.

Criteria for change of medical therapy

In addition to the DAS scores for skin (DAS-S) and muscle (DAS-M), obtained at the initial visit and each visit thereafter, the child with JDM was also assessed using a consistent panel of physical and laboratory tests at each visit. This evaluation included the Childhood Myositis Assessment Score (CMAS), performed by an experienced pediatric physical therapy team. Serologic tests included muscle enzymes (creatine kinase, lactic acid dehydrogenase, and aldolase), complete blood count, neopterin, von Willebrand factor antigen (compared with the normal range for the child's blood group), and flow cytometry evaluation of peripheral lymphocyte subsets. If the child's symptoms improved, and the laboratory tests were in the range of normal for age, then the IVMP (30mg/kg with one gram maximum) was slowly decreased in frequency, until it was discontinued, and then the prednisone was decreased by 1 mg/month, if the interval testing showed no reactivation. In contrast, if the child did not respond clinically and/or the laboratory parameters showed continued activation, then other medications were added. The following immunosuppressive therapy was continued when MMF was started: intravenous pulse methylprednisolone (n=15), methotrexate (n=38), hydroxychloroquine (n=19) and IVIG (n=4). During the 12 month course, because 5/50 (10%) children were still symptomatic or had abnormal laboratory values despite MMF in conjunction with the other medications, the additional medications were started/restarted: cyclosporine (n=1/1), IVIG (n=4/1), methotrexate (n=0/5), hydroxychloroquine (n=2/2), and intravenous methylprednisolone (n=2/5). At the 12 month follow-up visit, the following medications were continued to be used as treatments: intravenous pulse methylprednisolone (n=10), methotrexate (n=36) hydroxychloroquine (n=18), while more patients were receiving IVIG (n=8).

Statistical Analysis

We used mean, median, and standard deviation to describe continuous variable (e.g. age, duration of untreated disease, and others) and used proportions to summarize dichotomous variables (e.g. gender, race, etc). Linear mixed models were applied to analyze changes of DAS scores, prednisone dose, height and weight over time. Cochran-Mantel-Haenszel test and Poison regression were applied to assess changes of MMF infection rates over time. Wilcoxon Signed-Rank test was used for pair-wise comparison of prednisone dose, height and weight. Analyses were conducted using SAS 9.3 and 0.05 was used as the criteria for the level of statistical significance.

Results

Patients

The demographics and clinical characteristics for the 50 patients are presented in Table 1. The demographics are similar to previous reports from our center documenting a female bias (76%) with a predominately white (78%) population. At diagnosis, this group had a long duration of untreated disease (median=5 months), preceding the start of conventional therapy, which was given for a mean of 2.8 years before the start of MMF.

Disease activity

After start of MMF, the mean DAS-S decreased from 5.24 ± 0.29 to 4.20 ± 0.28 at 6 months ($p=0.003$) and 3.72 ± 0.29 at 12 months after start of MMF, ($p= 0.001$). Correspondingly, the DAS-M dropped from 2.44 ± 0.39 to 1.17 ± 0.28 ($p=0.002$) after 12 months of therapy, but not at 6 months (Figure 1). When the patients who received IVIG were removed from this analysis, and the data reanalyzed, the conclusions remained essentially the same: the DAS-S significantly decreased over 12 months ($p=0.0001$), DAS-M also improved ($p=0.02$). Specifically, compared to data at the start of MMF, the DAS-S was significantly lower at 6 months ($p=0.004$) and further improved at 12 months ($p<0.0001$). Similarly, DAS-M was significantly lower at both 6 months ($p=0.02$), but did not further change between 6 months and 12 months ($p=0.96$).

Medication requirements

The prescribed dose of prednisone (mg/kg/day) at MMF follow-up at both 6 and 12 months was significantly lower than that at the start of MMF therapy, dropping from 0.39 ± 0.06 mg/kg to 0.34 ± 0.05 mg/kg after 6 months of MMF ($p=0.044$) to 0.23mg/kg ± 0.02 ($p<0.0001$) at 12 months after start of MMF (Figure 2). The decrease in prednisone dose, as recounted in the methods section, was only instituted when all the laboratory data and the child's disease signs and symptoms were within normal limits.

Tolerability of MMF

Overall, patients tolerated MMF well and there were no serious adverse events attributed to MMF between onset and follow-up visit. None of our children stopped MMF because of toxicity. We used as an inclusion criteria for this study "12 months of therapy" in order to try to identify adverse reactions to MMF. Toxicity to MMF was not reported during the course of therapy, at the level of 20 mg/kg divided BID in the setting of the other drug therapy as noted. Two children reported some abdominal discomfort which resolved when the dose of MMF was lowered.

Infection rate

Forty-one out of 50 (82%) patients experienced 132 infections during the study period. The incidence of infections was 0.25/month before start of MMF, 0.21 infections per month in the first six months of MMF therapy, and 0.12 infections per month in the next six months (7–12 months). There was not a significant difference between the pretreatment and the *first 6 months* after the start of MMF therapy ($p=0.44$), but in the *second 6 months* (7–12) the infection rate was significantly lower than in the pretreatment data ($p=0.001$). The majority of these infections were viral upper respiratory infections (53%), followed by sinusitis and otitis media in 8.3% and 5.3%, respectively. Additional infections occurring in less than 5% of patients included herpes zoster, conjunctivitis, central line infection, thrush, dental abscess, skin abscess, infected calcification, urinary tract infection, strep throat and mononucleosis. No serious infection requiring hospitalization related to MMF occurred

during the study period, and none of the JDM children developed leucopenia or B cell abnormalities as measured by flow cytometry (data not shown).

Growth parameters

Using the method of least square means to compile the data for height and weight, the mean height of the children when MMF was started was 146.25 cm ± 3.69, and by 12 months later, their height had increased to 149.51 cm ± 3.69, p=0.016, while the mean weight increased as well, from 50.42 kg ± 3.31 to 53.25 kg ± 3.81, p=0.005.

Discussion

This is the first report that describes pediatric patients with JDM treated with MMF and followed for one year after start of therapy. The rationale for the use of MMF in this patient population was based on the finding that, like pediatric systemic lupus erythematosus (SLE) in which MMF has been effective (15), children with JDM have a documented a florid Type-1 interferon induced gene expression pattern (5,8,10). In addition, both patients with SLE and JDM have increased serum IFN-α activity as determined by the WISH reporter cell assay (11,24). After the pharmacokinetics and safety data for MMF had been obtained in children (23), MMF was reported to be an effective therapy for children with SLE (15). Some of the symptoms of JDM share similarities with SLE. For example, both have a vasculitic malar rash, although the SLE band test is not present in skin from children with JDM. Disease resistance to conventional therapy in JDM is characterized by persistence of skin involvement, often after the musculoskeletal symptoms normalize (13). Active skin disease at any level of severity in children with JDM has been associated with calcinosis development. A goal of the therapy is to control cutaneous inflammation, which may minimize this devastating complication (25).

In 2000, Gelber et al (26) described four adult patients with severe cutaneous disease related to dermatomyositis and improvement in skin manifestations following MMF. Subsequent case reports of adults with dermatomyositis, polymyositis, and myositis associated with connective tissue disease have suggested control of muscle inflammation by MMF (17,26–31). It is difficult to make direct comparisons of these studies given the different outcome measures utilized in the investigations, but improvement in weakness, creatine kinase (CK) or overall disease activity was not uncommon. Similarly, in our cohort we demonstrate a significant decrease in disease activity of both skin and muscle inflammation at follow-up. We did not report CK levels because children with long disease duration greater than four months are more likely to have muscle enzymes that are in the range of normal values (32).

Recent reviews (33,34) of the treatment of dermatomyositis include a discussion of MMF, and the authors report that they find MMF useful as a second choice adjunct treatment after methotrexate. Given the improvement in both skin and muscle DAS in our patients, we concur that MMF may be a beneficial option in children with JDM not responding to traditional therapy with corticosteroid and methotrexate. Since IVIG had been found to potentiate the effect of MMF (31), some of the more resistant cases received this therapy as well. In addition to disease activity improvement, we found that children receiving MMF were able to decrease the dose of corticosteroids. This finding is comparable with reports in adults with idiopathic inflammatory myopathy (16,17,27–31,34). In children, there is even greater concern to minimize corticosteroid exposure given their deleterious impact on growth and bone mineral accretion. We had demonstrated that prior to corticosteroid exposure; children with JDM had reduced lumbar spine bone mineral density (35), which could be intensified by the long term administration of corticosteroids.

Increased susceptibility to infection associated with the use of MMF was highlighted in a report by Rowin et al. (36) in which 3 of 10 patients with dermatomyositis developed opportunistic infections and resultant death in one patient. This is in contrast to our study, which did report infection as the most common side effect, but none of the patients had a serious infection requiring hospitalization. A study of patients with renal transplant receiving MMF as maintenance immunosuppression demonstrated no mortality from infection (18). Among adults with myositis receiving MMF, life-threatening infections were not reported (16,17,27–31,34,37–38). Gastrointestinal side effects can be associated with MMF, but in our cohort, only one child developed vomiting while taking the liquid form of MMF, which stopped when tablets were used. Caution in female patients of child-bearing potential is warranted, as MMF is contraindicated in pregnancy (39). Fortunately, none of the subjects in our cohort became pregnant and we advise practitioners to counsel female patients accordingly. A very rare but serious complication of MMF therapy, mentioned in a report of B cell lymphomas in three patients with SLE, was the occurrence of primary central nervous system lymphoma (PCNSL) in a single patient with dermatomyositis treated with MMF and methotrexate, which spontaneously resolved with discontinuation of both drugs (40). It is clear that because of the lack of controlled trials in patients with myositis, the role of MMF remains to be confirmed.

There are several limitations to this study: first is the retrospective study design; and second, is the lack of a concurrent control group of JDM, closely matched for age and disease severity, who had not been given MMF. Despite these limitations, we report the results of 50 pediatric patients treated with MMF, which is a robust sample size, given that JDM is a rare disease. We do not report therapeutic drug monitoring of MMF, as this remains controversial, even in the transplant literature. Further case-control pharmacokinetic studies in adult and pediatric subjects with myositis should be considered to better understand the role of therapeutic drug monitoring in this patient population.

In conclusion, MMF appears to be worthy of consideration as an additional therapeutic modality for the treatment of children with JDM. This study suggests that both skin and muscle manifestations respond to MMF in children with JDM, but the skin inflammation, which is often resistant to therapy, responds especially well. Therefore, MMF is steroid-sparing and offers an alternative therapy as well as minimizing corticosteroid exposure in children with JDM. MMF appears to be well-tolerated, but clinicians should judiciously monitor patients for infectious and hematologic complications. Randomized, controlled trials of MMF in patients with JDM would help to establish its role in the management of this often chronic and devastating disease.

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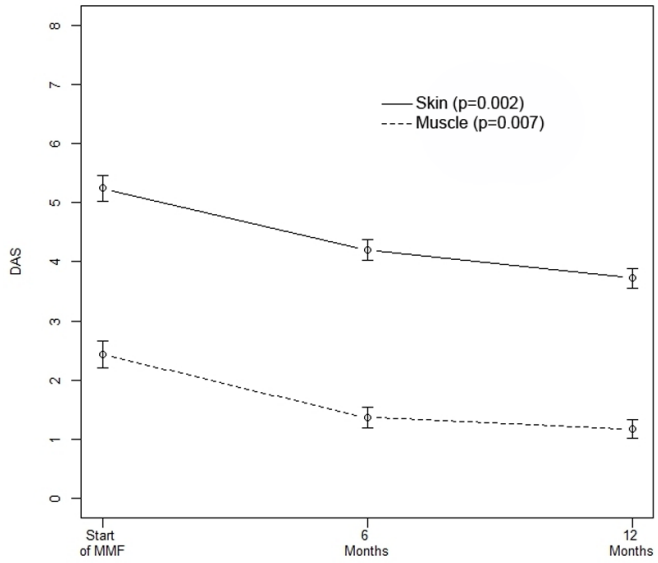

Figure 1.

DAS-S and DAS-M are significantly improved over 12 months of MMF therapy, with p-values of 0.002 and 0.007, respectively. The DAS-S is also significantly lower at six months (p=0.003) compared to the values before the start of MMF. Similarly, DAS-M was significantly lower at both 6 months (p=0.02), but did not further change between 6 months and 12 months (p=0.96). Bars show the mean and SEM.

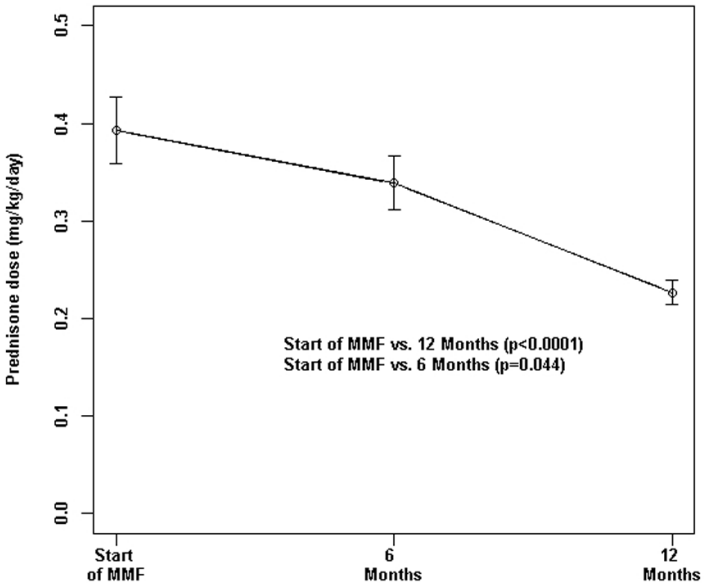

Figure 2.

Daily prednisone dose (mg/kg/day) at start of MMF was significantly higher as compared to follow-up visits. P-value* was determined by linear mixed modeling. Bars show the mean and SEM.

Table 1

Demographics and Clinical Characteristics

	n (%)	Age at MMF Start median yrs (min, max)	DUD* median mths (min, max)	Onset to MMF Start median yrs (min, max)	Dx** to MMF Start median yrs (min, max)
Gender					
Female	38 (76)	12.3 (4.6, 23.2)	4.5 (1.3, 113.8)	3.4 (0.2, 16.2)	2.8 (0.1, 15.2)
Male	12 (24)	12.9 (4.2, 17.1)	8.5 (1.1, 22.3)	3.6 (1.1, 10.5)	2.6 (0.2, 10.3)
Race					
White	39 (78)	12.9 (4.2, 23.2)	4.5 (1.3, 113.9)	4.1 (0.2, 16.2)	3.2 (0.1, 15.2)
Hispanic	10 (20)	11.4 (4.6, 16.5)	6.4 (1.1, 22.3)	2.4 (1.1, 10.5)	2.0 (0.2, 11.3)
Black	1 (2)	7.1 (7.1, 7.1)	9.4 (9.4, 9.4)	1.8 (1.8, 1.8)	1.0 (1.0, 1.0)
Total	**50 (100)**	**12.6 (4.2, 23.2)**	**5.0 (1.1, 113.8)**	**3.6 (0.2, 16.2)**	**2.8 (0.1, 15.2)**

*DUD = Duration of Untreated Disease

**Dx = Diagnosis